“A PROSPECTIVE, RANDOMIZED COMPARATIVE STUDY TO EVUALUATE THE EFFICACY AND SAFETY OF EPIDURAL BUPIVACAINE MORPHINE WITH KETAMINE VERSUS EPIDURAL BUPIVACAINE WITH MORPHINE ALONE FOR POSTOPERATIVE ANALGESIA AFTER MAJOR ABDOMINAL SURGERIES”

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MADRAS MEDICAL COLLEGE

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CERTIFICATE

This is to certify that the dissertation entitled, **"A Prospective, Randomized Comparative Study To Evualuate The Efficacy And Safety Of Epidural Bupivacaine Morphine With Ketamine Versus Epidural Bupivacaine With Morphine Alone For Postoperative Analgesia After Major Abdominal Surgeries"** submitted by Dr. P. KAYALVIZHI in partial fulfilment for the award of the degree of Doctor of Medicine in Anaesthesiology by the Tamilnadu Dr. M.G.R. Medical University, Chennai is bonafide record of the work done by him in the INSTITUTE OF ANAESTHESIOLOGY & CRITICAL CARE, Madras Medical College, during the academic year 2010-2013.

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CONTENTS

1INTRODUCTION

The first approach to the epidural space was the caudal approach by Jean Athanase sicard and Fernand cathelin independently in the year 1901.

Later in 1921 Fidel pages who was honoured as The Father of Modern epidural anesthesia described the inter spinous approach to the epidural space who identified it by tactile technique.

Ten years later in 1931, Achille M. Dogliotti of Turin identified the epidural space by loss of resistance technique.

The Famous Needle Tuohy was introduced by Edward Tuohy in 1945.

Later in 1949 Martinez curbelo of Havana used Tuohy needle and urethral catheter to perform the first continuous epidural anaesthesia.

But the PVC catheter with closed tip was introduced in 1962 which made the continuous epidural block and anesthesia easier.

The epidural blockade[3] is a type of segmental blockade where only the desired segments are blocked which differentiate it from spinal anesthesia and also the analgesia can be extended in the post operative period through the continuous catheters.

In the epidural space local anesthetics are always combined with adjuvants[27] like adrenaline, opioids, α2 agonists, neostigmine, magnesium sulphate, ketamine etc., to shorten the onset of action and to prolong the duration of analgesia in the post operative period.

Ketamine[35] has been added as an adjuvant in neuraxial blockade. It has both analgesic and sedative properties. It is a potent N – methyl D – Aspartate receptor antagonist which inhibits central sensitization due to peripheral nociception, thus potentiate the analgesic effects of morphine when administered with it.

Keeping this properties and interactions in mind we conducted a prospective randomized double blinded study to evaluate the efficacy and safety of epidural bupivacaine, morphine with ketamine versus epidural bupivacaine with morphine alone for post operative analgesia after major abdominal surgeries.

ANATOMY OF THE VERTEBRAL COLUMN WITH SPINAL CORD

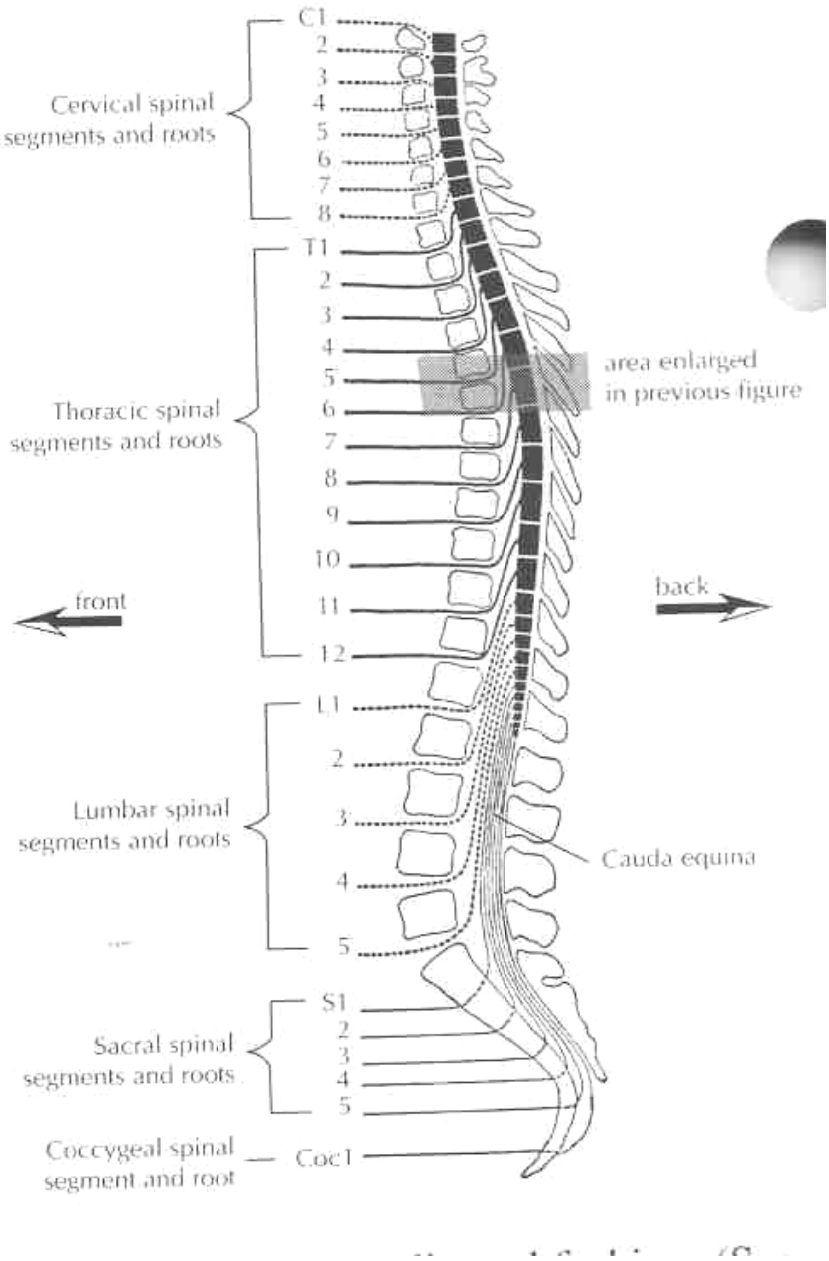


Fig. 1

ANATOMY OF EPIDURAL SPACE

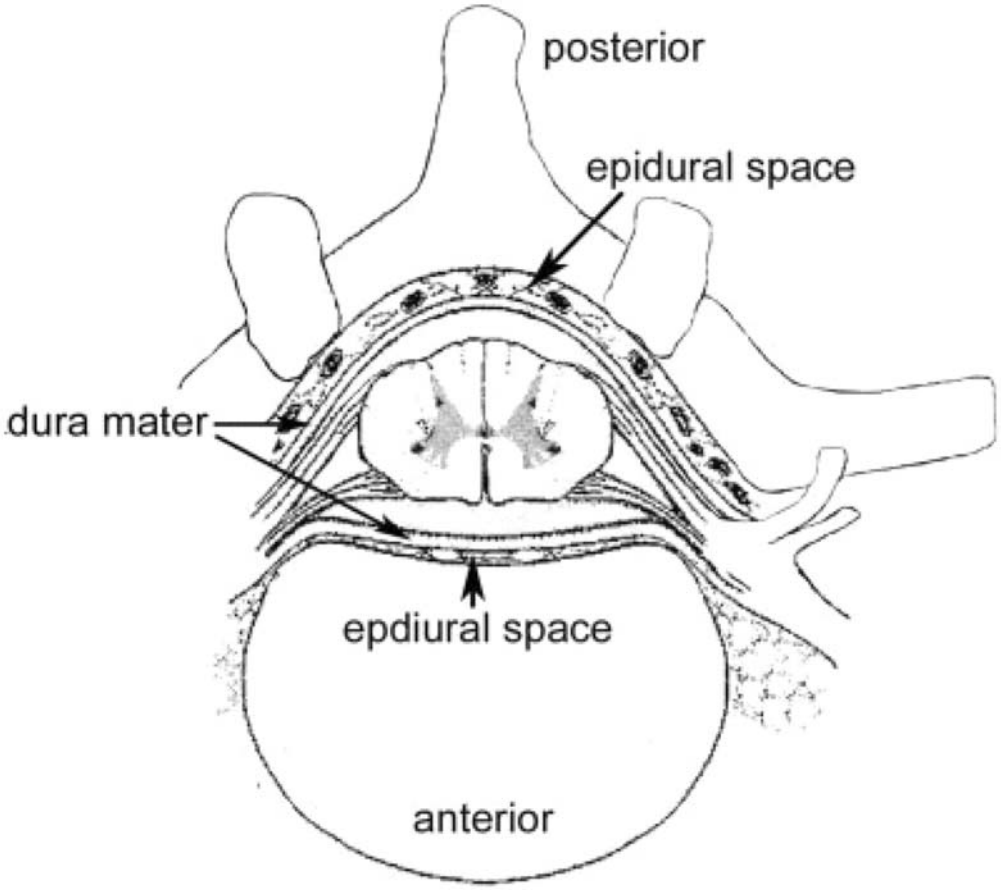


Fig. 2

There are 7 cervical, 12 thoracic, 5 lumbar, 5sacral and 4 coccygeal vertebrae that form the vertebral column. The spinal canal is formed by the adjacent vertebral formina. The canal provides support and protection to the spinal cord and its nerve roots. Normally the spinal cord extends from the foramen magnum to the L1L2 vertebral level in adults & L3 level in children. There are eight cervical ,12

thoracic, 5 lumbar and 5 sacral and 1 coccygeal pair of spinal nerves. The spinal cord and its root are surrounded by three layers of membrane, inner most in the piamater. The second layer is the arachnoid mater and the space between the piamater and arachnoid mater is the subarachnoid space filled with cerebrospinal fluid. The outermost layer is the duramater and the space between the arachnoid and the duramater is the subdural space and finally the space out side the dura mater is the extradural (or) epidural space .We have to pass through skin, subcutaneous tissue, supra spinous ligament, inter spinous and ligamentum flavum for performing an epidural block.

PICTURE OF EPIDURAL BLOCK:

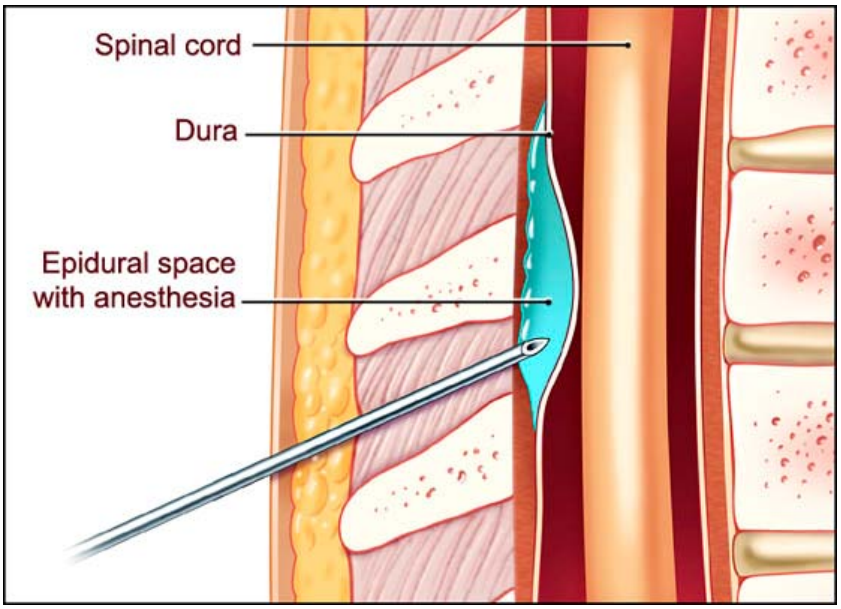


Fig. 3

ANATOMY OF EPIDURAL SPACE[2] :

It is a potential space which extends from the base of skull to the sacral hiatus and surrounds the duramater anteriorly, laterally and posteriorly. It has the following boundaries

1) ligamentum flavum posteriorly

2) Pedicles and

3) Intervertebral foramina laterally.

Epidural space is smaller than the sub arachnoid space.

CONTENTS OF THE EPIDURAL SPACE:

Fat, areolar tissue, lymphatics, veins and nerve roots are present in the epidural space, without any free fluid. The volume is more in obese people and less in elderly people, due to reduction in the epidural fat there by leading to reduction in dose requirements. Also is obese patients and pregnant females there is increased chance of catheter migration due to compression of Inferior venacava and also due to continuation of Bateson's plexus of veins with iliac veins in the pelvis and azygos veins of thorax and abdomen.

Usually, the distance of the epidural space from the skin is about 4.5-5cm in 75-80% of individuals and also varies at different vertebral levels.

Vertebrae	**Distance from skin to ligament (cm)**	**Thickness of ligament (mm)**
Cervical vertebrae	-	1.5-3.0
Thoracic vertebrae	-	3.0 – 5.0mm
Lumbar vertebrae	3.0 – 8.0	5.0 – 6.0 mm
Caudal	variable	2.0-6.0mm

EPIDURAL ANALGESIA

INDICATIONS

1) As an adjuvant to general anesthesia, and also it will reduces the opioid and other analgesic requirement is the intra operative period. Eg.

- Gynaecologial surgeries
- Abdominal
- Thoracic
- Vascular sugeries

2) For analgesia alone (eg. Labour analgesia). It will not produce motor blockade, and it is not sufficient for performing surgery.

3) As a sole technique for surgical anesthesia eg. Lower segment caesarian sections, urological surgeries, Lower limb surgeries and lower abdominal surgeries

4) Management of chronic pain is terminally ill patients and treatment of back pain eg. Epidural steroid.

5) Post operative analgesia

After a surgery, it is used as a sole anaesthetic (or) used is

Combination with general anesthesia

And post operatively with the help of catheters, in the epidural space.

CONTRA INDICATIONS:

The absolute contra indications are

- patient refusal
- raised intra cranial tension
- infection at the site of injection
- hypovolemia & shock

The relative contra indicationss are

- Coagulopathy
- spine deformity
- neurological disorders.

Site effects

- Local anaesthetic toxicity and allergy
- Hypotension
- Inadervent high blockade
- Epidural abscess, hematoma, meningitis

- Post dural puncture headache
- Anterior spinal artery syndrome
- Arachnoiditis
- transverse myelitis
- Catheter migration into the epidural vessels.

POST OPERATIVE PAIN[3]

It is worse and it has deleterious effect in almost all systems of the body

1) In the cardio vascular system the pain causes increase is heart rate , blood pressure, increase is systemic vascular resistance and cardiac work. This may precipitate angina and myocardial infarction is susceptible individuals.

2) In the Respiratory system, hypoxia, hyper carbia, atelectasis, decreased vital capacity and cough to clear the secretions resulting in ventilation perfusion mismatch and other complications.

3) In the gastro intestinal system, vomiting and ileus will occur.

4) In the renal system, urinary retension and decreased urine output will occur.

5) There will be increased risk of thromboembolism due to pain and limited mobility.

6) In the endocrine system, there will be symphathetic stimulation, hyper metabolim and increased oxygen comsumption.

7) And finally in the central nervous system anxiety, fear and fatigue will occur.

THE ADVANTAGES OF POST OPERATIVE EPIDURAL ANALGESIA:

The reduction in vital capacity in upper abdominal surgeries are around 75% where as in lower abdominal surgeries it is around 50 – 55%. So thoracic epidural analgesia provides effective pain relief thereby improving vital capacity and other pulmonary functions .

In the cardio vascular system it will reduce blood loss, transfusion requirements, reduce the incidence of angina, myocardial infarction and deep vein thrombosis.

In the endocrine system reduction in the level of catcholamines and over all reduction in morbidity, mortality and duration of hospital stay.

VARIOUS PHYSIOLOGICAL EFFECTS OF EPIDURAL BLOCKADE[4]:

The site of action of local anesthetic in the epidural space is the spinal verve roots.

The segmental nerve roots in the thoracic and lumbar regions are mixed nerves containing somatic sensory,motor and autonomic nerve fibres.

Sensory blockade interrupts the transmission of both somatic and visceral painful stimuli where as motor blockade provides muscle relaxation with varying degrees of sympathetic blockade.

The injection site for epidural anaesthesia should be close to the target nerve roots to obtain better results.

The important concept for epidural anesthesia is a differential nerve block. It means the nerve fibres with variable function demonstrate a varying sensitivity to the effects local anesthetics.

The order of blockade in epidural anesthesia are sympathetic blockade, then pain temperature, proprioception followed by motor blockade .

Usually following an epidural block, the sympathetic blockade particularly temperature vary from 1-4 segments higher than the motor blockade, where as regression of level occurs in reverse order.

Effects in the CVS:

The effect depends on the level of blockade. Vasomotor tone is maintained by T5 – L1 sympathetic fibers which innervate vascular smooth muscles.

When there fibres are blocked, arterial and veno dilatation with pooling and decreased systemic vascular resistance will occur.

Effects in the respiratory system:

It has minimal effect in patients with adequate lung function.

All lung volumes like tidal volume, vital capacity and minute ventilation and dead space are unchanged.

There will be no alteration in pulmonary function, even with high thoracic blockade.

Even in intercostal paralysis by a high thoracic block major alteration is not seen.

Effects in the gastro intestinal system:

Due to blockade of sympathetic fibres from T5 – L1 there will be an unopposed vagal action lead to increase in peristalsis and a small contracted gut.

Renal system:

Epidural anesthesia has little effect on renal function due to auto regulation of renal blood flow, though urinary retention is common.

Mechanism of Action of local anaesthetics in the epidural space:

In the epidural space local anesthetics bind to sodium channels, in the inactivated state preventing further activation of the channel and development of action potential. They block the sodium and potassium ion channels in the dorsal horn and they inhibit the generation and propagation of pain signals and produce similar action is the ventral horn also. In the spinal cord, calcium channels one blocked producing resistance to stimuli from nociceptive afferent neurons and there by producing analgesia. Also the local anaesthetics inhibit the release of

substance P and other neuro transmitters like glutamate, calcitonin gene related peptide (CGRP) neurokinin I& II) in the epidural space and therefore inhibit pain signal transmission.

FACTORS AFFECTING THE ACTION OF LOCAL ANESTHETICS IN THE EPIDURAL SPACE:

Site of injection:

There is equal spread of local anaesthetics in the thoracic epidural space and cranial (or) cephalad spread in lumbar epidural space.

1) **Volume:** 1- 5 – 2ml per segment for lumbar segment and 1- 1.5ml per segment for thoracic segments.

Age:

In old age the inter spinous spaces become narrowed due to calcification of ligaments lead to reduced dose requirements.

Weight:

Obese individuals and pregnant females require less volume because of space narrowing and venous engorgement.

Height:

Shorter individuals require lesser volume.

Alkalinisation of local anesthetics

Alkalinisation (high PH) potentiates the onset of action.

Posture has little effect.

Adjutvants

Addition of adjuvants enhance the quality of blockade eg) opioids, alpha2 agonist,ketamine etc.

Common techniques of epidural block

Usually in sitting or lateral decubitus position, through midline (or) paramedian approach.

Needle

18 (or) 16 G 9cm Tuohy's needle and tip is called on Hueber tip which has 15 – 20 degree angulations to guide the catheter.

LOSS OF RESISTANCE TECHNIQUE

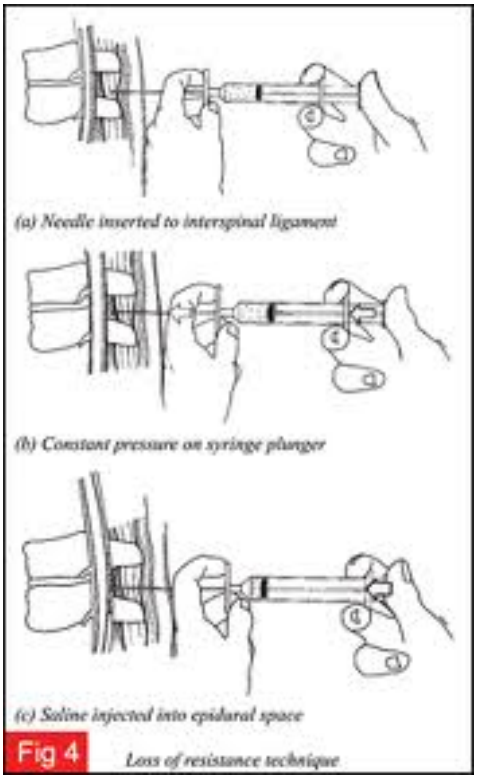


Fig. 4

EPIDURAL CATHETER

TUOHY 'S NEEDLE

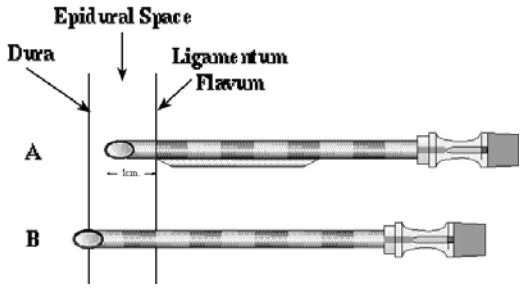


Fig. 5

HUEBER TIP

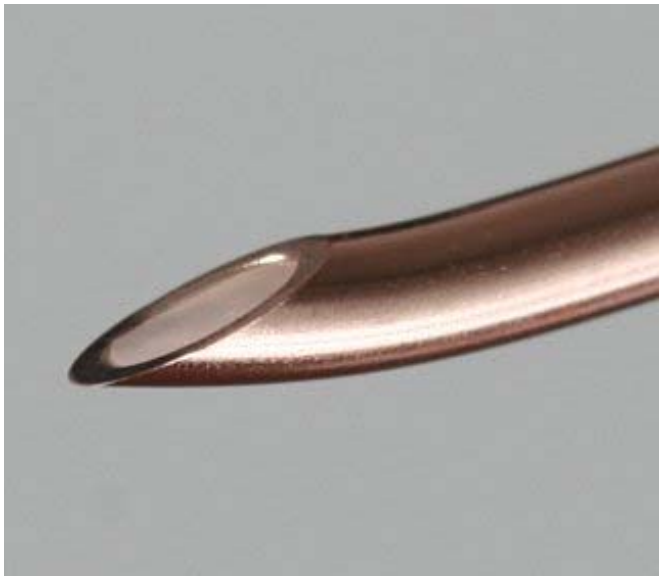


Fig. 6

Various methods of identifying epidural space:

- Loss of resistance technique. It is the most commonly used method. LOR with air (or) saline and the test is called as whoosh test,but there is risk of air embolism in children.

- Hanging drop method

- Recently a pressure transducer used saline filled sterile tubing is connected to the epidural needle,and if the needle tip enters into the space, the pressure will drop suddenly. This is useful in obese

patients and identifying epidural space in the cervical region.This is called as epidural space identifier.

- Modified drip method (1991)
- Macintosh epidural balloon (2008)
- Epidural (it is an optimal pressure loss of resistance device) (2011)
- Finally neuraxial ultrasonography recently developed for identification of epidural space (2010). and
- Epiduroscopy.

EPIDUROSCOPY

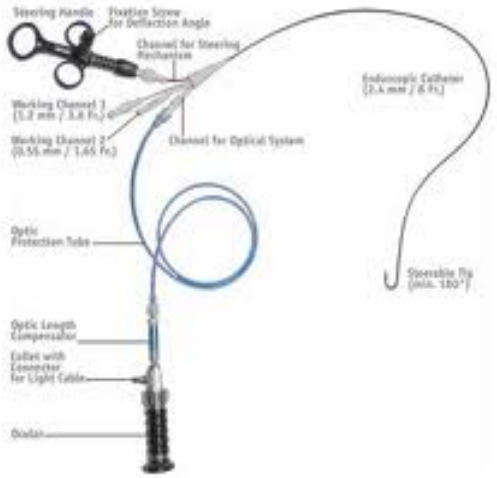


Fig. 7

PHARMACOLOGY OF BUPIVACAINE

Bupivacaine[6] in an amide local anaesthetic formed by addition of butyl group to the piperidine nitrogen of mepivaccine.

It contains equal proportions of 'S' & 'R' enantiomers and a racemic mixture is obtained.

Chemical Structure

±I butyl N- (2, 6 dimethyl phenyl) -2-piperidine

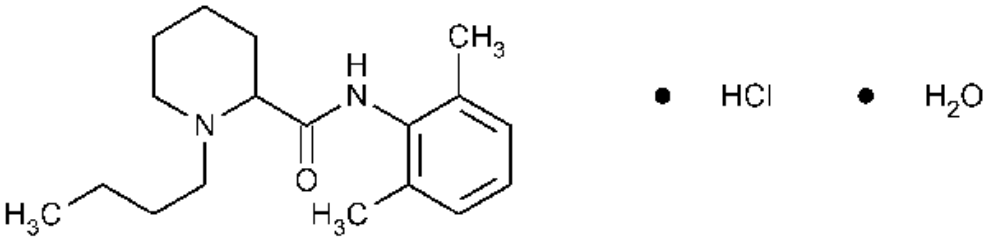


Fig. 8

Dacar boxamide hydrochloride monohydrate

Physico chemical Profile

Molecular weight	-	288.
PKa	-	8.1.
Plasma protein binding	-	95%.
Lipid solubility	-	28.
VD	-	71hrs.

Clearance	-	0.472/min
Onset	-	Slow
Duration	-	240 – 480 min
Potency	-	4
Toxic plasma concentration	-	240 -480min
Elimination HL	-	210min

Mechanism of action:

They produce conduction blockade by selectively binding to alpha subunit of sodium channel, in an activated closed state , and prevent their change to rested closed and activated open state there by preventing conduction of impulses and action potential.

In addition to sodium channels bupivacaine blocks voltage dependent potassium channels and this leads to broadening of action potential.

Bupivacaine also blocks the L type calcium channels.

In addition bupivacaine blocks both types of pain fibres myelinated A –delta and C fibres. Preganglinic-B fibres are readily blocked by local anaesthetics.

Pharmaco dynamics

Bupivacaine has a stabilizing action on all excitable membranes. So in the cardio vascular system it causes a reduction in automaticity and in the nervous system restlessness, tremors and convulsions occur on over dosage. It is more potent than lignocaine, the sensory blockade in more than the motor blockade.

Pharmacokinetics

Bupivacaine is a weak base that has a PKa value above the physiological PH and therefore only a small fraction of the drug is in ionized form.

Rapidly absorbed from the site of injection, dose and addition of adjuvants and the plasma concentration depend on the route of administration (5 -30min) ,distribution and rate of clearance.

The lungs are capable of extracting bupivacaine from the systemic circulation and its first pass pulmonary extraction is dose dependent.

Metabolism:

Bupivacaine binds to the plasma protein alpha-1-acid glycoprotein.

It undergoes aromatic hydroxylation, N dealkylation, amide hydrolysis & conjugation. The nes methyl bupivaccine is measured in the blood and urine after epidural administration. Renal diseases will not affect the kinetics of bupivaccine and only < 10 -15% of the drug is excreted unchanged in urine.

Uses of bupivacaine

- For central neuraxial block (Spinal epidural and caudal)
- Peripheral nerve block
- Infiltration anaesthesia

Preparations available

0.25%, 0.5% in vials (10ml) (o to 20ml) 5mg/ml + dextrose in 4 ml ampoules,

Maximum permitted dose 3mg/ml for		Con 0.25 - 0.5%
Maximum 150mg	for	0.75%-
Maximum 20 mg	for	0.5%

Side effects are

- allergy
- pruritus
- urticaria
- angioneurotic edema
- accidental intra vascular injection.
- CNS toxicity:
- tinnitus
- vertigo
- drowsiness
- muscle twitches,
- slurred speech,
- seizures
- coma .
- Cardiac toxicity:
- Hypotension
- Arrhythmia
- Atrio ventricular block
- Ventricular tachy cardia
- Ventricular fibrillation
- hepatotoxicity

PHARMACOLOGY OF MORPHINE[6]

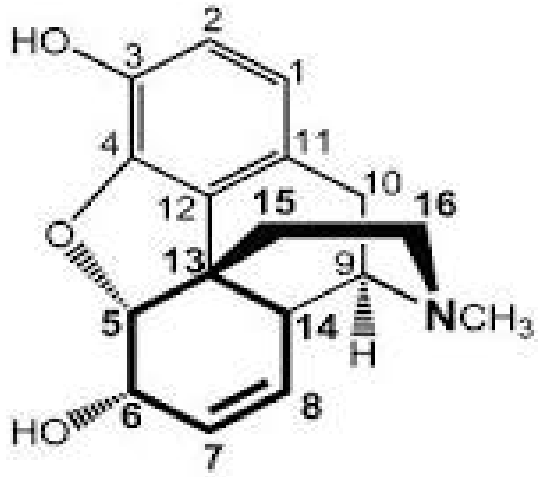


Fig. 9

It is the naturally occurring phenanthrene oploid alkaloid. It is an mu1 mu2 & K receptor agonist. These stereo specific opioid receptors are present in the presynaptic and post synaptic sites in the central nervous system , in the brain stem , spinal cord and other peripheral tissues.

Morphine is unique in producing analgesia without loss of touch, proprioception and unconsciousness.

Mechanism of action

Opioid receptor activation leads to decrease in neuro trans mission i.e Pre synaptic inhibition of neuro transmitters like

Acetylcholine, Nor epinephrine dopamine, substance P and also post synaptic inhibition of evoked potential increased Potassium conductance ie.hyperpolarisation and finally results in calcium channel inactivation.

Pharmacokinetics:

Absorption: Rapidly absorbed after im injection and peak plasma level is reached after 20 -60 min.

Distribution: Distribution half life is rapid (5 -20 min) it has low lipid solubility and slow passage across the blood brain barrier so its onset of action is slow and duration is prolonged. Its action is terminated by redistribution but large doses depend on bio transformation to lower their plasma levels.

Biotransformation: Morphine undergoes conjugation with glucuronic acid to form morphine -3- glucronide (75 – 85%) and morphine- 6- glucuronide(5 -10%).

Excretion: The end products are excreted by kidneys and only <10% by biliary excretion. About 5 -10% of morphine is excreted unchanged in urine. Renal failure prolong the duration of morphine. The

accumulation of morphine metabolites like morphine-3-glucuronide and morphine-6 glucuronide in patients with renal failure will produce narcosis and respiratory depression but morphine -6- glucuronide is a potent opioid than morphine.

EFFECT ON ORGAN SYSTEMS:

Cardio vascular system

High doses are associated with vagally mediated bradycardia decrease in arterial blood pressure, vasodilation, decrease in sympathetic reflexes. Rarely it evoke histamine release. The combination of opioid with other vasodilators, Volatile, N20, Benzodiazepines and barbiturates lead to significant myocardial depression.

Respiratory System :

It depress ventilation particularly respiratory rate. Rarely Paco2 increased. The apnoeic threshold and highest paco2 at which a patient remain apnoeic is elevated and hypoxic drive is decreased. Rarely histamine release lead to broncho constriction during airway instrumentation.

Central nervous system:

Decrease thecerebral 02 consumption, cerebral blood flow and Increase the Intra cranial pressure → stimulation of medullary chemo receptor trigger zone is responsible for nausea and vomiting. Repeated opioid administration in higher doses is associated with dependence.

Gastro intestinal system:

Slows gastic emptying and peristalsis, causes contraction of sphincter of oddi produces biliary colic.

Endocrine system:

Stress hormones are decreased. So ischemic heart disease patients may benefit from attenuation of stress response.

Neuraxial Morphine;

Act through mu receptors in the substantia gelatinosa of the spinal cord. They are specific for visceral than somatic pain. Analgesia is due to the ascend of the drug across the dura to gain access to the mu receptor.

Pharmacokinetics:

Morphine in the epidural space may undergo uptake in epidural fat, systemic absorption (or) diffuse into the dura into the CSf. Peak effect of morphine after epidural administration is 10 – 15min and it depends on lipid solubility.

Side effects of neuraxial morphine:

- Pruritus
- Nausea
- Vomiting
- Urinary retention and
- depression of ventilation.

Dose of Neuraxial morphine:

- Epidural single dose 1-5mg, continuous infusion 0.1 – 1 mg/hr
- Pre medication Im - 0.05 -0.2mg/kg
- Intra operative analgesia iv 0.1 – 1mg/kg
- Post operative Im - 0.05 – 0.2mg/kg
- Analgesia Iv- 0.05 – 0.15 mg/kg.

Clinical uses:

- Analgesia in sub anaesthetic doses
- for induction (iv) in higher doses
- neuraxial anaesthesia and analgesia.

PHARMACOLOGY OF KETAMINE[6]:

It is a N-METHYL –D –ASPARTATE receptor antagonist.

Structure of ketamine

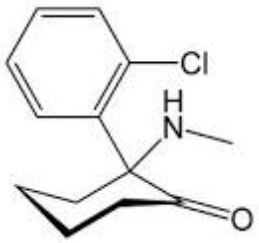


Fig. 9

THREE DIMENTIONAL STRUCTURE OF KETAMINE:

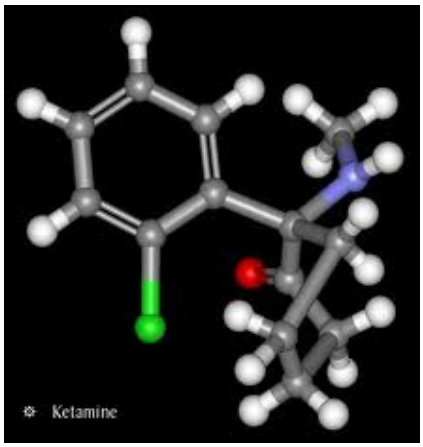


Fig. 10

It is a phencyclidine derivative and it produces dissociative anesthesia. ketamine is water soluble and it is produces profound analgesia in sub anaesthtic doses.

Structure:

The presence of asymmetrical carbon atom result is existence of two optical isomers of ketamine.

The S (+) ketamine (lefthanded optical isomer) & R (+) Ketamine Right handed optical isomer. The S (+) ketamine produces more intense analgesia more rapid metabolism, recovery, less salivation and less incidence of emergence reactions.

Mechanism of action:

Ketamine binds non competitively to the phencyclidine recognition site on NMDA receptors and inhibits activation of NMDA receptor by glutamate and decrease the pre synaptic release of glutamate which potentials the effects of neurotransmitter gamma amino butyric acid. The inter action with phencyclidine is more with S (+) ketamine.

Pharmaco kinetics:

It has rapid onset of action, shorter duration of action and high lipid solubility. Ph 7.5 peak concentration 1min after intra venous injection and 45min after intra muscular injection. I has high blood solubility and rapidly transferred across the blood brain barrier. Ketamine induced increase in cerebral blood flow facilitates rapid achievement of high brain concentration and then it is redistributed from the brain to other highly perfused and less well perfused organs. It has a high hepatic extraction ratio , large volume of distribution and elimination half life of about 2 -3 hrs.

Metabolism

Metabolized by hepatic microsomal enzymes ie. Cytochrome p450 enzymes to form Norketamine. This nor ketamine contributes to prolonged effects of ketamine (analgesia). The Nor ketamine is hydroxylated, then conjugated to form water soluble, inactive glucronide metabolite and excreted by the kidneys.

Neuraxial Ketamine:

Ketamine has been reported to interact opioid receptor. When we combine ketamine with opioid and local anaesthetics it will produce additive (or) synergistic effect.

Site effects:

In the central nervous system it increases cerebral blood flow and CMRO2 and increase intra cranial pressure.

It produces emergence delirium due to depression of of medialgeniculate and inferior colliculus. In the cardio vascular system sympathetic stimulation lead to increase in heart rate and blood pressure. In the respiratory system it produces bronchodilatation and bronchorroea but it has a protective effect against bronchospasm. Hepatic diseases have less effect on its metabolism.It inhibits platelet aggregation.

Doses:

For induction iv-1-2mg/kg,im 5-6mg/kg. epidural 0.12-0.5mg/kg maximum upto 1mg/kg.

REVIEW OF LITERATURE:

1. Mamta Sethi[7,20] et al ,

Conducted a study to evaluate the effect of adding small dose ketamine for patient controlled epidural analgesia post operatively. The study group was about 100 patients posted for major upper abdominal surgery of age group 18 – 65yrs of ASA I & II PS were randomly allocated into two groups. After extubation the patient was shifted to PACU, where using ten point VAS score (Visual analgesia scale) pain intensity was assessed. If VAS >3 an initial dose of 0.125% of bupivacaine of 10ml was administered epidurally and then PECA pump was attached. Group I – received Bupivacaine 0.625% and morphine sulphate (preservation free 0.05 mg/ml Group II – Received Bupivacaine 0.625% and morphine (preservation free 0.5mg/ml) and ketamine hydrochloride (preservation free 10.2mg/ml). The mean morphine consumption in group I in the first and second post operative day was 8.38 ± 2.85 and 7.65 ± 1.95mg in group II. Which was statistically significant ($P < 0.05$) and also pain relief after 6,12,24, and 48 hours (at rest and movement) was better in group II than group I ($p < 0.05$).

2. Wong CS[9] et al,

Conducted a study to evaluate the analgesic efficacy of epidurally administrated ketamine and morphine in the post operative period. The study was done in 40 patients posted for major joint replacement surgery of ASA I & II. For primary anaesthetics epidural lignocaine was used. These 40 patients were divided with two groups.

Group A → Received 10 ml of saline

Group B → Received 10 mg ketamine

Group C → Received 2 mg morphine

Group D → Received 10mg ketamine plus 0.5mg morphine.

The intensity of pain, incidence of any side effects and number of intra muscular meperidine (1mg/ml) were recorded. The results were co administration of ketamine and morphine 0.5mg produced intense analgesia and conclusion was ketamine potentiates the analgesic effect of morphine especially when it is administered as a pretreatment and also it reduced the dose of morphine needed and reduced the incidence of side effects.

3. Taylor Brandao schnaider[8] et al,

They conduced a study to evaluate the effect of epidural ketamine, clonidine and dexmedetomidine in patients posted for upper abdominal surgery. The study was a Ramdomised double blind study, included 70 patients of ASA I, II physical status of age group 18 – 60 years, both gender, posted for sub costal chole cystectomy, under general anesthesia with lumbar epidural anesthesia. They were divided with 4 groups, where control group received 20ml of 0.75% ropivacaine and 1 ml of normal saline.(n= 10) .Ketamine group received 20 ml 0.75% ropivacaine and 0.5mg/kg ketamine (n=20) ,Clonidine group received 20ml of 0.75% ropivacaine and 1ml of clonidine(150micg) (n=20) and finally Dexmedetomidine group received 20ml of 0.75% bupivacaine and 2mg/ml dexmedetomidine (n=20). In all the groups anesthesia was induced with etomidate, alfentanil and rocuronium and maintained with sevoflurane and alfentanil. Analgesia was evaluated by clinical sings and inspired concentration of the inhaled anaesthetic agent by anaesthetic gas analysis during surgery. All the patient received ketamine clonidine and dexmedetomidine have had heart rate and systemic blood decrease and not required analgesics and the inspired concentration of isoflurance were 0.5 – 1%. Finally they concluded,

epidural ketamine, clonidine and dexmedetomidine when administered is the intra operative period, decreased alfentanil consumption and isoflurane inspired concentration.

4. Yoko Kawana[10] et al,

They conducted a study in 60 patients undergoing abdominal gynaecological surgery. They were randomly divided into 6 groups,

1) Control group received saline
2) Ketamine 4mg
3) Ketamine 6mg in saline
4) Ketamine 8mg in saline
5) Ketamine 6mg in 10% glucose
6) Morphine 3mg,

In all the groups anesthesia was induced with thiopentone, nitrous oxide with O2 and enflurane, the drugs were given epidurally in the post operative period . The results were the duration of analgesia in the ketamine group did not differ from that in the control group and difference in diluent had no effects. The patients in the morphine group needed no analgesia and pain relief was adequate where as patients is other 5 groups needed analgesia. The conclusion was ketamine alone was inadequate for pain relief after gynaecological surgeries.

5. Ching Yue Yang[18] et al,

Conduced a study to evaluate the effect of ketamine on spinal morphine is terminal concer pain. They conduced this study in 2 groups. In group I – intrathecal morphine alone given twice daily. In group II – intrathecal morphine and ketamine (10ml) twice daily and dose of morphine is titrated based on numeric raring scale for pain relief and rescue dose of morphine was less than (0-10) 5mg, after each intrathecal administration for two days. The results were effective intrathecal morphine was higher in morphine group (I) than Group II. The average pain scales reduced in group II than group I after the effective dose of morphine has reached. and finally the conclusion was that ketamine potentiates the analgesic effects of morphine there by reducing the dose of intrathecal morphine.

6. CT Wu[21] et al,

Conducted a randomized single blinded study to evaluate the benefits of pre emptive analgesia for upper abdominal surgery using preincisional epidural bupivacaine and morphine and ketamine for achieving post operative pain relief.

Study group was about 60 patients posted for upper abdominal surgery of ASA I & II were divided into 3 groups. Group I – received general anesthesia followed by epidural infusion of normal saline. Group II & III patients received general anesthesia with continuous epidural infusion of lignocanie 2%. Thirty minutes after infusion group I & II are gives ketamine 10mg + morphine epidurally. In group III ketamine and morphine and bupivacaine given 10 min after 2% lignocaine injection and 30 min before skin incision. All these patients received epidural pain control regimen for 3 days. During this period duration of analgesia (PCA)morphine consumption pain intensity at rest and movement adverse effects were recorded and finally the conclusion was pre incisional epidural ketamine, morphine and bupivacaine combined with continuous epidural anesthesia and general anesthesia gives better post operative pain relief than post incisional ketamine, morphine plus bupivacaine.

7. Aida Sumihisa[12] et al,

Conducted a randomized double blind study to evaluate the effect of pre emptive analgesia by intra venous low dose ketamine and epidural morphine in gastrectony surgeries. Patients posted for gastrectony were divided into 3 groups.

Group I- Received preemptive epidural morphine

Group II- Received preemptive IV ketamine

Group II- Received preemptive epidural morphine + pre emptive IV ketamine.

Post surgical pain relief, morphine consumption were recorded. The results were, pre emptive epidural morphine + IV ketamine provided intense analgesia and reduction in morphine consumption and reduced incidence of side effects ($p < 0.05$).

8. Manzo Suzuki[13] et al,

Conducted a study to evaluate the effects of co administration of low dose ketamine (50 – 100micg/kg) enhance morphine (50micg/kg) induced analgesia after out patient surgery.

140 patients undergoing out patient surgery were selected and divided into 4 groups. In all the 4 groups injection midazolam 1-2mg was given and induced with propofol 2-2.5mg/kg and maintained with N20- O2 mixture and desflurane .

Group I - Received morphine 50 micg/kg with placebo.

Group II- Received morphine 50micg/kg + ketamine 50micg/kg IV.

Group III- Received morphine 50 micg/kg + ketamine 100micg/kg IV.

In all the 4 groups pain intensity was measured using VAS score, in the recovery room, then every 5 min until the time of discharge and morphine consumption were recorded. Finally the conclusion was small dose ketamine 75 – 100 micg/kg enhanced morphine induced analgesia after out patients surgery.

9. Subramaniyam[14,22,23] et al,

They conduced a prospective randomized double blinded study to evaluate the efficacy of epidural ketamine plus morphine compared with epidural morphine alone for post operative pain relief after major upper abdominal surgery. In this study, the study population was divided into 2 groups.

Group I - Received epidural morphine 50mg/kg

Group II- Received epidural morphine 50 mg/kg + ketamine 1mg/kg post operatively. These patients were followed up for 48 hrs and results were recorded. The onset of analgesia was

shorter and duration was longer in group II than group I (P < 0.05) and mean morphine consumption in group II was also less than group I. and they concluded the addition of epidural ketamine 1mg/kg to epidural morphine 50micg/kg gave better analgesia after major upper abdominal surgery.

10. Lawretti[15] GR et al,

Conducted a randomized double blind study to study the analgesic effects of low dose ketamine, neostigmine and midazolam to epidural morphine in terminal cancer pain patients. About 48 patients were divided into 4 groups. All the patients were receiving oral amitryptilline 5omg at bedtime. Pain was initially treated with epidural morphine 2mg B D to maintain VAS score below 4/10 and then if VAS > (or)=4.

Just after epidural morphine control group received epidural morphine 2mg. ketamine group received 0.2mg/kg epidural ketamine in 2ml. Neostigmine group received 100micg epidural Neostigmine in 2ml. Midazolam group received 500micg epidural midazolam in 2micg.

The result were recorded the conclusion was addition of low dose epidural ketamine or epidural Neostigmine to epidural morphine increases the duration of analgesia and less side effects (P< 0.05).

11. H. Choe[11] et al ,

Conducted a study to evaluate the efficacy of preincisional epidural morphine and ketamine versus post incisional epidural morphine and ketamine in patients posted for upper abdominal surgery. In the pre incisional group epidural ketamine 60mg and morphine 2mg were given before induction of anesthesia. In the post incisional group epidural ketamine 60mg and morphine 2mg were given after removal of the surgical specimen. The results were recorded and the conclusion was preoperative administration of epidural morphine and ketamine provided more effective post operative pain relief than it was given during the intra operative period.

12. Elshobary HM[16] et al,

Conducted a study to evaluate the usefulness of epidural ketamine in patients undergoing major abdominal surgery.Patients >65years were divided into 2 groups. Group I received pre emptive epidural bupivacaine 0.125% (20ml) combined with epidural ketamine 40mg and post operatively a bolus of 0.125% Bupicacaine 5ml supplemented with 2mg/ml ketamine. Group II received pre emptive epidural bupivacaine 0.125% (20ml) combined with epidural morphine 2mg and post

operatively a bolusof 0.125% Bupivacaine 5ml supplemented with morphine 0.1mg/ml until a pain score of 2 was achieved. The analgesia, sedation and side effects were recorded.The conclusion was patients in ketamine group were associated with less side effects and sedation, required more frequent and continuous analgesia ($p< 0.05$). Patients in morphine group required less analgesics and experienced more side effects.

13. Ravat[17] et al,

Conducted a study in 20 patients undergoing orthopaedic or lower abdominal surgery. They were divided into 2 groups and they were trained in assessing post operative pain score. For group I- 0.05 – 0.1 mg/kg morphine was given epidurally. For group II 4 -6 micg/kg ketaminewas given epidurally. Pain scores RR, BP & side effects were recorded. They concluded that there was no improvement in pain scores in patients with ketamine group and complete failure of ketamine to produce analgesia in groupII than group I (morphine).

14. YY Chia[19,20] et al,

Conducted a double blinded study to evaluate the effect of adding small dose ketamine in a patient control regimen. The study group (91

patients for major surgery) were divided into 2 groups. For group I post operatively with PCEA device morphine 0.02mg/kg, bupivacaine 0.8mg/ml, ketamine 0.4mg/ml and epinephrine 4micg/ml were given. For group II post operatively with PCEA device morphine 0.02mg/kg, Bupivacaine 0.8mg/ml and epinephrine 4micg/ml were given. The result were recorded. In group I there was better pain relief and reduction in morphine consumption and less side effects than group II. The conclusion was addition of small dose ketamine to morphine gave better post operative analgesia.

15. Mohammed Naguib[25,26] et al,

Conducted a study to evaluate the effect of intra muscular versus epidural ketamine in patients (34) posted for gall bladder surgery for post operative pain relief. Group I received 30mg im ketamine group II received 10mg ketamine in 10ml saline epidurally. Group III received 30 mg ketamine in 10ml saline epidurally. The patients were followed up for 24 hrs, and ketamine was given on patient's request. The result were recorded and the conclusion was 30mg epidural ketamine provided better post operative analgesia.

16. M lak et al

Conducted a double blinded randomized study in 50 kidney donars receiving morphine as analgesics were selected and divided into two groups. One group received ketamine, And the other group received saline. Post operative pain was assessed by measuring morphine consumption and pain scores for 48 hrs after surgery.

Result: Pain intensity and morphine consumption were less in the ketamine group.

Conclusion: Post operative analgesia was better with ketamine and a significant decrease in morphine consumption.

17. Arati[24] et al,

Studied the effect of adding epidural morphine with two different doses of ketamine for post operative analgesia after abdominal hysterectomy.

It was a randomized double blinded study.Adequate pain relief and early mobilization in the post operative period were assessed.Finally the authors concluded that the synerstic effect of combining morphine 30mic/kg with ketamine 0.2mg/kg epidurally provided good analgesia and early mobilization with lesser side effects.

AIM OF THE STUDY

Comparative evaluation of the safety and efficacy of epidural bupivacaine with morphine and ketamine VS epidural bupivacaine with morphine alone for post operative analgesia after major abdominal surgeries.

MATERIALS AND METHODS:

After approval of the study by our institutional ethical committee ,the study was conducted in 60 patients of ASA1&2 undergoing elective abdominal surgeries.

Materials:

- Largygoscopes with blades of various sizes, bougie, oropharyngeal airway.
- Drugs - thiopentone, fentanyl, atracurium, glycopyrrolate, neostigmine, xylocard, succincylcholine and all emergency drugs, Injection bupivacaine, morphine, preservative free ketamine.
- Monitors – NIBP. ECG, Spo2
- Syringes 5ml, 10, 20ml.
- 18G intravenous cannula.
- Appropriate size endotracheal tubes.
- Epidural catheter, Tuohy’s needle.

Inclusion criteria:

- Age:18-65 yrs.
- ASA:1 & 11.
- Surgery:Eledctive abdominal surgery.
- Who have given valid informed consent .

Exclusion criteria:

- Not satisfying inclusion criteria.
- Patient posted for emergency surgery.
- Contraindication for regional blockade.
- Known sensitivity to the drugs.
- Pregnant females.
- History of opoid addiction.
- History of psychologi9cal disorder.
- ASA >2.

The patients who fulfilled the above explained criteria were taken into the study after obtaining informed consent from them.

PRE OPERATIVE ASSESSMENT AND RECORDING OF VITALS:

The age, weight, height and vital parameters like pulse rate, blood pressure and baseline investigations like haemoglobin, blood sugar, urea, creatinine, chest x-ray, ECG were checked. Thorough examination of all the systems and airway assessment were done.

Methods:

60 patients of age group 18 to 65 years of ASA physical status 1 & 2 posted for major abdominal surgeries are selected and randomly allocated into 2 groups. Patients were shifted inside the operating room. Monitors were connected. The base line blood pressure, heart rate and oxygen saturation were recorded. Under strict aseptic precautions , Prior to induction of anaesthesia epidural catheter was placed in T8-t10 intervertebral space using Tuohy's, needle with loss of resistance technique and the test dose of 3ml of 1.5% lignocaine was given through the epidural catheter. In both the groups anaesthesia was induced with thiopentone 5mg /kg and fentanyl 2 mic/kg, intubated with atracurium 0.5 mg/kg and anaesthesia was maintained with atracurium 0.1mg/kg and Volatile Nitrous Oxygen mixture. Intra operative

analgesia was maintained with intermittent doses of fentanyl. After end of procedure reversal of residual neuromuscular blockade with neostigmine 50mic/kg and glycopyrrolate 10 mic/kg, then the patient was shifted to PACU .(post anaesthesia care unit)

Monitoring in the PACU:

In the PACU the patient was assessed for pain intensity using the 10 point vas score.

Visual analogue scale[VAS] was explained to patients.The patients were shown a 10 cm long scale marked 0-10cm on a blank paper and told them 0 represented NO PAIN and 10 represented WORST POSSIBLE PAIN .

VAS SCORE:

0-DOES NOT HURT

2-HURTS JUST A LITTLE BIT

4-HURTS ALITTLE MORE

6-HURTS EVEN MORE

8-HURTS A LOT

10-HURTS AS MUCH AS U CAN IMAGINE

IF the VAS score was more than 2 epidural was activated.The total volume was 12-14 ml in both the groups.

Group p-1 0.125% bupivaccine with morphine 0.05- 0.1 mg/kg with max dose 5mg and ketamine 0.2-0.5mg/kg with maximum dose of 1mg/kg. Group-2 0.25% bupivaccine with morphine 0.05-1mg/kg with maximum dose of 5mg. In both groups the following parameters recorded.

1. Onset of analgesia
2. Duration of analgesia
3. VASscore
4. Sedation score.

Monitoring of vitals:

Heart rate, systolicblood pressure, diastolic blood pressure and mean blood pressures at 0 min, 15 min, 30 min, 1hr, 2hr, 4hr, 6hr, 8hr, 12hr, 16hr, 20 and 24hr intervals.

Rescue analgesic requirements were recorded for 24 hrs.

Recording of adverse events:

The adverse effects like pruritus, respiratory depression, nausea, vomiting. hallucinations and delirium were recorded.

Primary outcome measures:

- Onset of analgesia.
- Duration of analgesia.
- Pain at rest and movement at0.15min.30min.1,2,4,6.8, 12,16,20, 24 hrs.
- VAS score, sedation score.(Ramsay sedation score) 1.patient anxious,agitated and ressless.2.cooperative,oriented and tranquil.3.responds to commands.4.exhibits brisk response to light glabellar tapor loud auditory stimulus.5.exhibits a sluggish response to light glabellar tap or loud auditory stimulus.6.exhibit no response.
- Rescue analgesic requirement

Secondary outcome measures:

- Heart rate.
- Systolic blood pressure
- Diastolic blood pressure
- Mean arterial pressure.

In both the groups the onset of analgesia,the duration of analgesia using VAS score,systolic ,diastolic and mean blood pressures ,heart rate,rescue analgesic requirements,incidence of complications were recorded for 24 hrs.

One or two patients had vomiting ,were managed with Inj. ondansetron 8mg intravenously .One or two patients had hypotension, [fall in systolic blood pressure more than 30% from base line were managed with iv fluids and incremental doses of Inj. ephedrine 6 mg iv. None of the patients experienced hallucinations or delirium.

OBSERVATION AND RESULTS:

Statistical analysis was done using Statistical package for social sciences (SPSS) windows version 15.The results were expressed here as mean and standard deviation.All qualitative variants were compared using chi square test and quantitative variants using student "t test.A p value of < 0.05 was considered as significant.

Demographic data:

The two groups were comparable with respect to age,weight,sex and ASA physical status as in tables 1-4.There was no statistically significant difference among two groups in demographic profile.

Table-1

Sex distribution of the Sample

Sex	Group-I N=30		Group-II N=30		P value
	N	%	N	%	
Male	14	46.67	14	46.67	1.00
Female	16	53.33	16	53.33	

Of the 60 patients 30 were males and 30 were females.The distribution was similar in both group of patients.

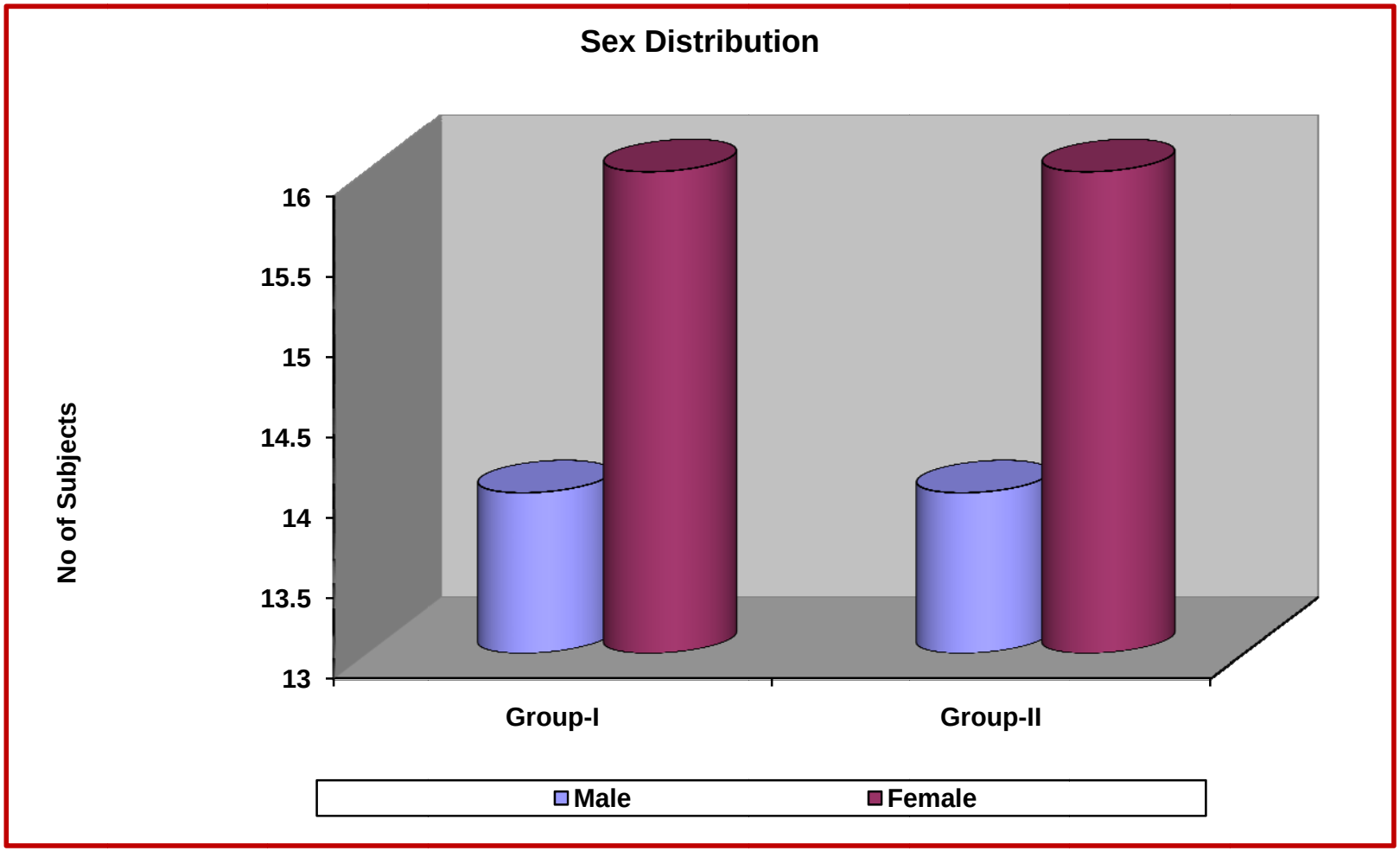

Sex Distribution
No of Subjects
16
15.5
15
14.5
14
13.5
13
Group-I
Group-II
Male
Female

Table-2

Age Distribution

Age group	Group-I		Group-II	
	Number	**Percentage**	**Number**	**Percentage**
20 - 30	1	3.33	6	20.00
30 - 40	8	26.70	9	30.00
40 - 50	11	36.70	8	26.70
50 - 60	7	23.30	7	23.30
60 – 70	3	10.00	0	0
Mean ± sd	46.33 ± 10.20		41.70 ± 10.81	
p-value	0.09 (Not Significant)			

The age distribution between the two groups were comparable.

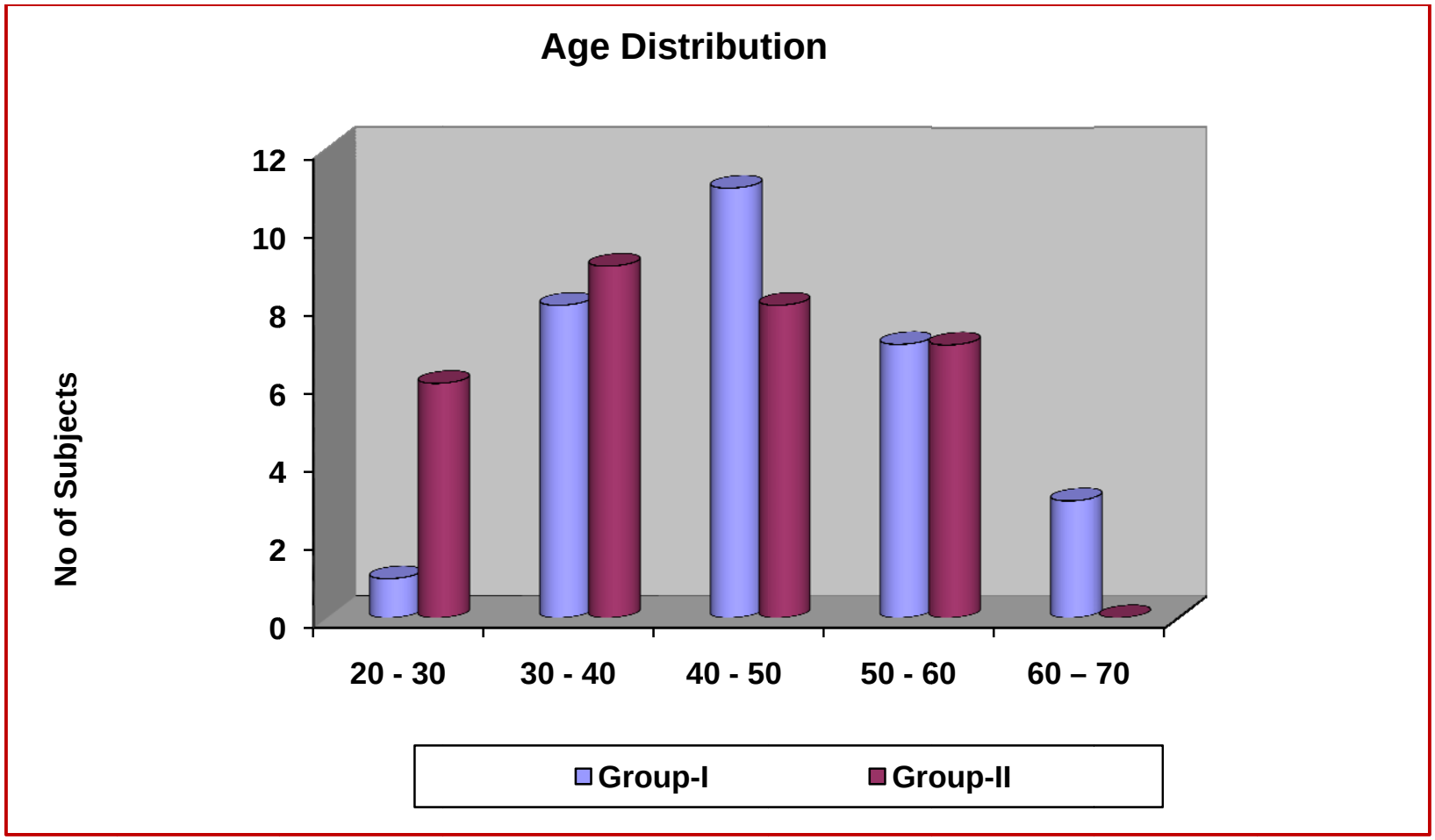

Age Distribution
No of Subjects
12
10
8
6
4
2
0
20 - 30
30 - 40
40 - 50
50 - 60
60 – 70
Group-I
Group-II

Table-3

Weight Distribution

Weight	Group-I		Group-II	
	Number	**Percentage**	**Number**	**Percentage**
40 - 50	2	6.70	2	6.70
50 - 60	25	83.30	20	66.70
60 – 70	3	10.00	6	20.00
70 – 80	0	0	2	6.70
Mean ± sd	57.23 ± 3.93		58.60 ± 6.49	
p-value	0.33 (Not Significant)			

The weight distribution between the two groups was also comparable.

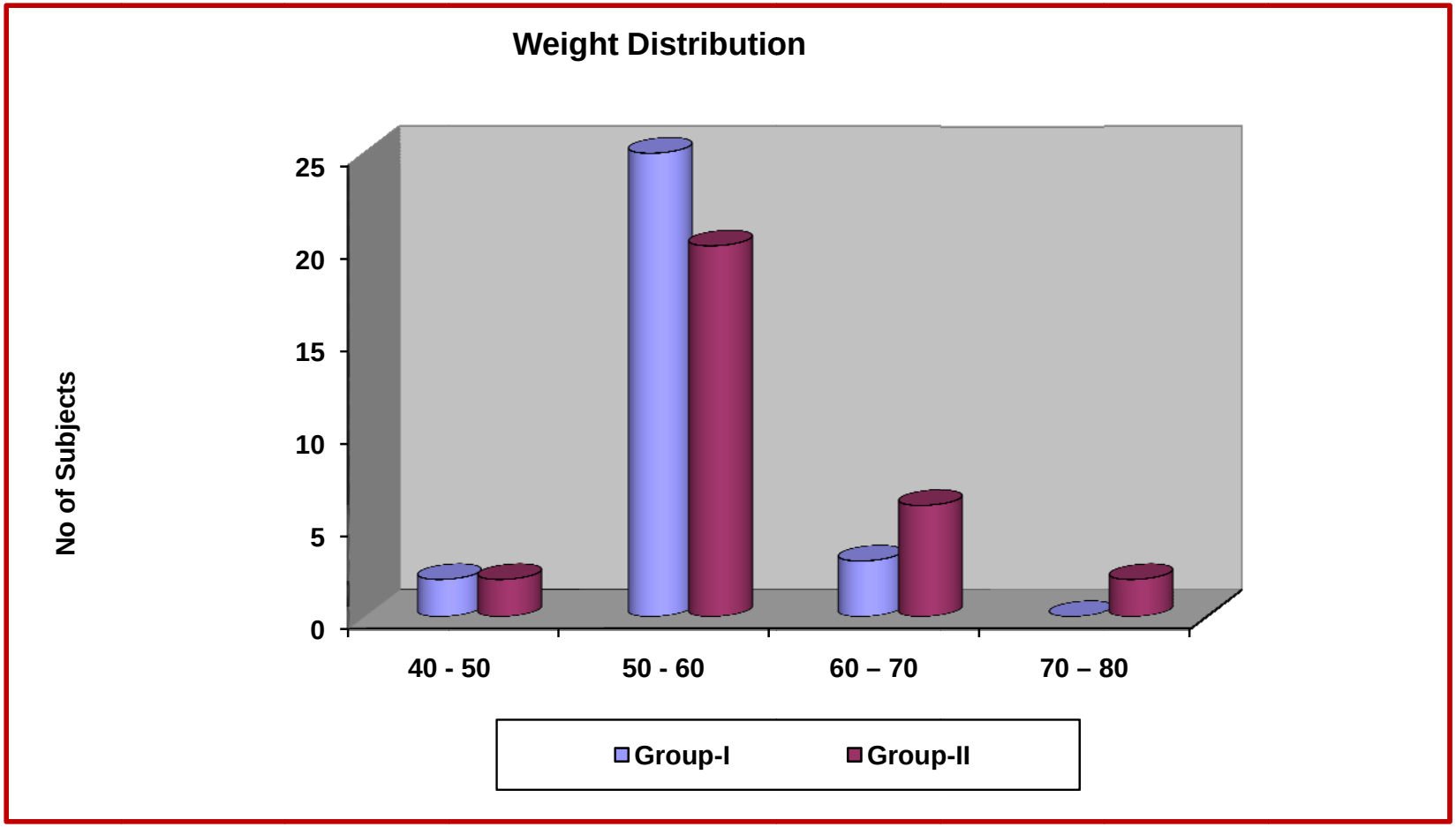
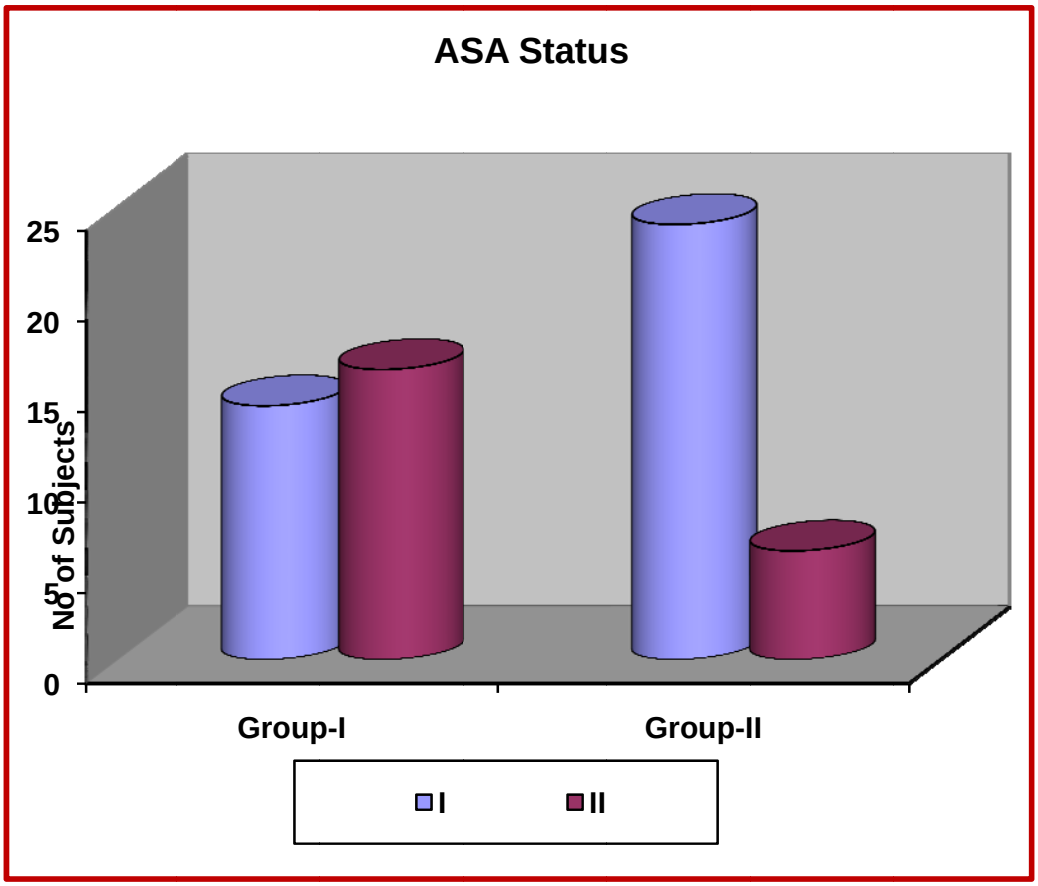

Weight Distribution
No of Subjects
25
20
15
10
5
0
40 - 50
50 - 60
60 – 70
70 – 80
Group-I
Group-II

Table-4

ASA STATUS

ASA	Group-I		Group-II		Total	
	N	%	N	%	N	%
I	14	46.67	24	80.00	38	63.33
II	16	53.33	6	20.00	22	36.67
Total	30	100	30	100	60	100
p-value	0.007 (Significant)					



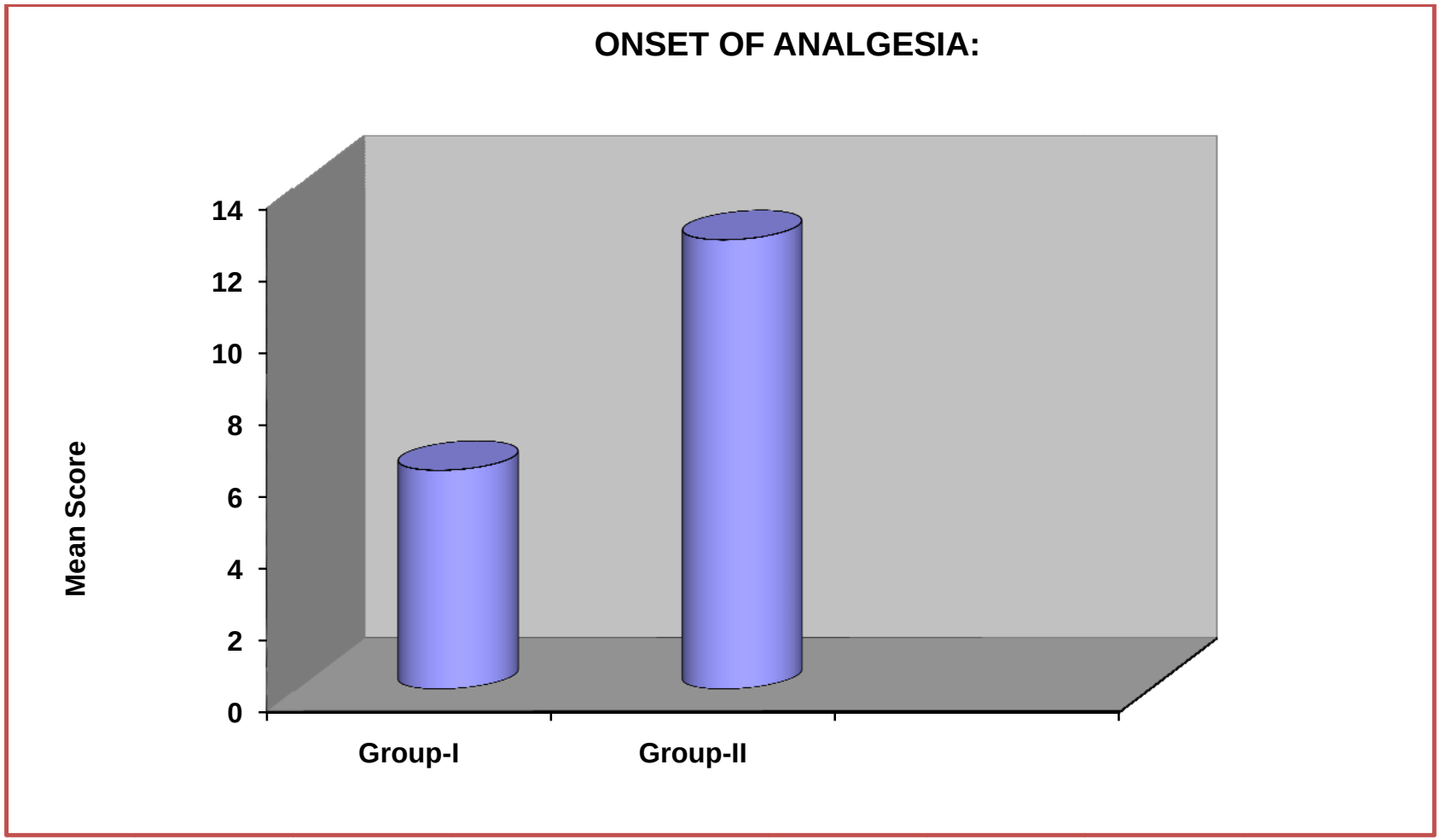
ONSET OF ANALGESIA:

Table-5

Onset Drug

	Group-I	**Group-II**
Mean ± sd	**6.10 ± 1.27**	**12.53 ± 2.08**
Range	5 - 10	9 - 15
p-value	0.000 (Significant)	

The mean onset of analgesia was 6.10(min) in group-I and 12.53(min) in group-II.It was statistically significant with a p value of 0.001.


ONSET OF ANALGESIA:
Mean Score
14
12
10
8
6
4
2
0
Group-I
Group-II

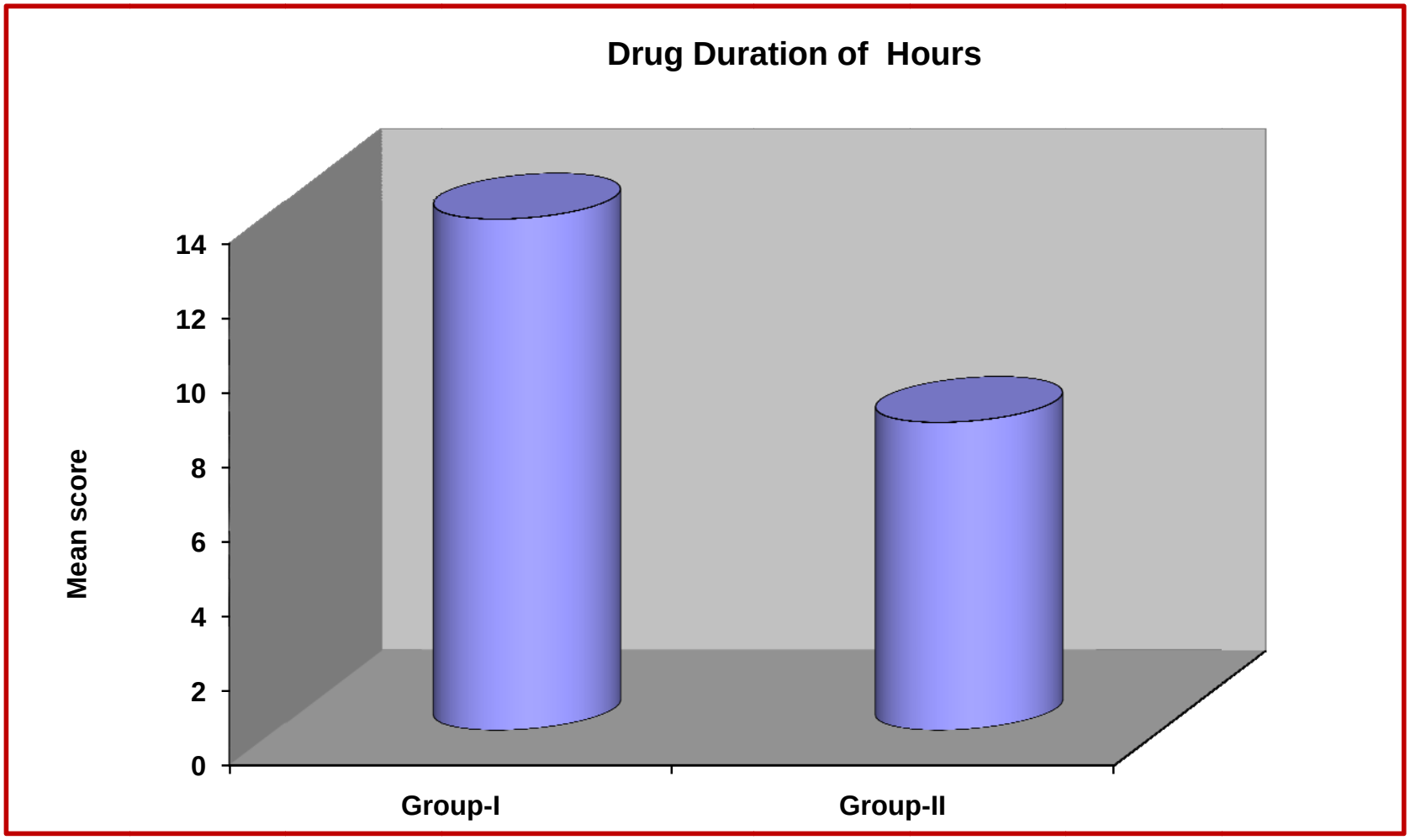
The drug duration of hours:

The mean duration of analgesia was 13.73(hrs) in group-I and 8.27(hrs) in group –II.

Table-6

Drug Duration of Hours

	Group-I	**Group-II**
Mean ± sd	**13.73 ± 3.10**	**8.27 ± 1.08**
Range	6 - 18	6 - 10
p-value	0.000 (Significant)	


Drug Duration of Hours
Mean score
14
12
10
8
6
4
2
0
Group-I
Group-II

VAS SCORE:

The median VAS score was 1 in group-I upto the mean duration of 13.73hrs and 1 in group-II upto the mean duration of 8.27 hrs as shown in table-7.

SEDATION SCORE:

The median sedation score was 2 in group II upto the mean duration of 13.73hours and the mediann sedation score was 2 in group I upto the mean duration of 8.27 hours. It is comparable between the two groups.

Table -7

Visual Analog Scale (Median)

Time	**Group-I** Median	**Group-II** Median
0 Min	3.00	4.00
15 Min	1.00	1.00
30 Min	1.00	1.00
1 hour	1.00	1.00
2 hour	1.00	1.00
4 hour	1.00	1.00
6 hour	1.00	1.00
8 hour	1.00	1.00
12 hour	1.00	3.00
16 hour	3.00	3.00
20 hour	3.00	2.00
24 hour	3.00	2.00

Haemodynamic variables:

The haemodynamic variables like heart rate,systolic blood pressure,diastolic blood pressure and mean blood pressures are comparable between the two groups.

Table-8

Heart rate:

Time	**Group-I** Mean	SD	**Group-II** Mean	**SD-II**	**P-value**
Base Line	83.33	**6.42**	76.67	**14.85**	**0.03**
0 Min	89.20	5.16	87.93	**9.48**	**0.52**
15 Min	79.10	5.93	78.07	**5.50**	**0.49**
30 Min	77.17	**5.29**	75.87	**4.79**	**0.32**
1 hour	77.00	4.72	77.00	**4.53**	**1.00**
2 hour	75.70	5.44	76.33	**4.33**	**0.62**
4 hour	77.40	5.09	76.03	**3.93**	**0.25**
6 hour	76.97	5.79	74.57	**3.36**	**0.05**
8 hour	77.33	6.69	79.60	**6.19**	**0.18**
12 hour	80.27	7.79	89.03	**8.12**	**0.000**

16 hour	87.40	7.74	90.97	**10.50**	**0.14**
20 hour	85. 80	9.02	89.33	**10.37**	**0.16**
24 hour	84.73	10,55	81.23	**9.25**	**0.18**

Table-9

Systolic blood pressure:

Time	**Group-I** Mean	**Group-I** SD	**Group-II** Mean	**Group-II** Sd	**P-value**
Base Line	125.60	12.22	124.27	10.94	**0.66**
0 Min	130.87	7.50	127.80	08.40	**0.14**
15 Min	120.73	7.27	118.60	6.26	**0.23**
30 Min	116.00	7.28	115.00	5.40	**0.55**
1 hour	113.67	5.87	113.07	4.03	**0.65**
2 hour	112.13	5.87	112.67	05.62	**0.96**
4 hour	111.50	4.97	110.73	3.91	**0.51**
6 hour	111.27	0.42	110.47	2.56	**0.41**
8 hour	110.47	4.51	116.67	08.70	**0.0.001**

12 hour	113.67	8.66	126.50	**9.41**	**0.000**
16 hour	120.73	8.15	123.87	**9.57**	**0.18**
20 hour	122.27	9.55	**124.17**	**8.17**	**0.41**
24 hour	119.87	8.37	**121.00**	**8.45**	**0.60**

Table-10

Diastolic Blood Pressure

Time	**Group-I** Mean	**Group-I** SD	**Group-II** Mean	**Group-II** SD	**P-value**
Base Line	78.07	9.15	77.13	7.89	0.67
0 Min	86.93	6.72	86.13	6.52	0.64
15 Min	78.33	5.07	76.67	5.95	0.25
30 Min	76.73	4.28	74.80	4.44	0.09
1 hour	75.27	4.41	73.20	4.16	0.07
2 hour	74.67	3.12	72.80	3.18	0.03
4 hour	73.40	3.41	72.43	3.13	0.26
6 hour	73.13	4.16	72.40	2.70	0.42
8 hour	73.23	3.82	74.87	6.14	0.22
12 hour	73.93	5.620	84.13	7.72	0.000

16 hour	79.97	6.92	858.93	7.36	0.002
20 hour	81.77	5.68	81.73	5.89	0.98
24 hour	79.30	5.68	78.80	5.52	0.73

Table-11

MEAN BLOOD PRESSURE

Time	**Group-I** Mean	**Group-I** sd	**Group-II** Mean	**Group-II** sd	**P-value**
Base Line	93.77	8.67	92.83	7.93	0.67*
0 Min	101.60	5.69	99.97	6.12	0.28*
15 Min	92.40	4.66	90.60	5.41	0.17*
30 Min	89.80	4.16	88.20	3.96	0.13*
1 hour	87.97	4.89	86.47	3.63	0.14*
2 hour	87.17	3.40	85.93	85.93	0.14*
4 hour	86.17	3.24	85.13	2.92	0.20*
6 hour	85.90	3.60	85.07	2.42	0.30*
8 hour	85.63	3.62	88.73	6.09	0.02
12 hour	87.23	5.78	98.23	6.40	0.000
16 hour	93.60	6.09	98.53	6.16	0.003
20 hour	95.20	5.13	95.93	4.34	0.55*
24 hour	92.87	4.97	92.83	5.24	0.98*

Table - 12

Incidence Of Complications

	Group-I		Group-II		Total	
	N	**%**	**N**	**%**	**N**	**%**
No complication	29	96.67	30	100	59	98.33
PRU	1	3.33	-	-	1	1.67
p- value	**0.31 (Not Significant)**					

Table-13

Rescue Analgesic Requirements

Time	Group-I		Group-II		P-value
	Not Required	**Required**	**Not Required**	**Required**	
2 hour	30	-	30	-	-
4 hour	30	-	30	-	-
6 hour	29	1	21	9	0.05
8 hour	26	4	0	30	0.001
12 hour	10	20	1	29	0.003
16 hour	1	29	2	28	0.55
20 hour	2	28	4	26	0.39
24 hour	14	16	21	09	0.07

DISCUSSION

The primary aim of the study was to evaluate the effect of adding low dose epidural ketamine with bupivacaine and morphine for post operative analgesia after major abdominal surgeries.

Our study population was around 60 patients of ASA I&II .We added ketamine 0.2mg/kg to morphine 0.05mg/kg in 12ml of 0.125% bupivacaine in one group versus morphine 0.05mg/kg in 0.125% of bupivacaine in the other group epidurally for post operative analgesia.We monitored the patients for 24 hrs from o min,15 min,30min,1 hrs,2hrs,4hrs,6hrs,8hrs,12hrs,16hrs,20hrs and 24 hrs.

Onset and duration of analgesia:

- The addition of low dose epidural ketamine to morphine accelerates the onset and the duration of analgesia results in effective postoperative analgesia.This correlates well with the previous studies done by Mamta sethi et al,Subramaniam et al and Wong CS et al. The mean time ofonset of analgesia was6.10(min) in group I& 12.53(min) in group II.The mean duration of analgesia was 13.73(hrs) for group_I and 8.27(hrs) for group-II.

- Mamta sethi et al studied the effect of adding low dose epidural ketamine to epidural morphine for post operative analgesia in 100 patients and this was done in PCEA (patient control epidural analgesia). They used a continuous infusion of 0.0625% bupivacaine ,morphine and ketamine for one group and 0.0625% bupivacaine and morphine for one group, and the patients were monitored for 48hrs and they calculated mean morphine consumption in each group for 48 hrs.But in our study we used a bolus of 0.125% bupivacaine,morphine and ketamine for one group &0.125% bupivacaine and morphine for one group and the patients were monitored for 24 hrs.Our primary outcomes like shorter onset and prolonged duration strongly correlates with the study conduted by Subramaniam et al.In their study they evaluated the effficacy of combination of epidural ketamine with epidural morphine in accelerating onset and duration of analgesia and strongly correlates with our study.

Stable haemodynamics:

- Our secondary outcomes like stable hemodynamics, reduced rescue analgesic requirement, less incidence of opioid related side effects etc., correlates well with other studies conducted by Ching Yue Yang et al,Wong CS et al,Lawretti et al and Yoko Kawana et al Arati et al.

- In the study conducted by Wong CS et al they concluded that ketamine though not an epidural anaesthetic agent ,it potentiates the analgesic effect of morphine when administered along with it ,without altering haemodynamics and an increase in the incidence of side effects.This strongly supports our study.

- In the study conduted by Yokokawana et al they concluded that ketamine alone administered was inadequate for pain relief.

- In the study conducted by Elshobary et al they evaluated the side effects between morphine group and ketamine group. Then concluded When compared to morphine group ketamine group experienced less side effects.This strongly correlates with our study.

- In the study conducted by Arati et al ,they concluded that the synergestic effect of combining morphine with ketamine epidurally provided good analgesia,early mobilization with less side effects.This strongly correlated with our study.

- In the study conduted by Ravat et al they concluded that ketamine alone is insufficient when administered epidurally ,even it procuced less side effects. It also supports our study.

SUMMARY

We conducted a rondomised double blinded study in a group of 60 patients belonging to ASAI& II undergoing elective abdominal sugeries to evaluate the effect of adding low dose epidural ketamine to epidural bupivacaine and morphine. Two groups of 30 each were randomly taken and analysed. The summary of our study are

- The two groups were comparable in terms of demographic profile such as age, sex, weight and height.

- The mean time of onset of analgesia was 6.10(min) in group-I versus 12.53 in group-II. It was statistically significant with a P value of 0.001.

- The mean duration of analgesia was 13.73(hrs) in group-I versus 8.27(hrs) in group-II. It was statistically significant with a P value of 0.001.

- The median VAS score was 1 in group-I upto the mean duration of 13.73hrs and was 1 in group –II upto the mean duration of 8.27hrs. ,and is comparable between two groups.

- The haemodynamic variables like heart rate,systolic,diastolic and mean blood pressures were comparable between the two groups.

The incidence of morphine induced side effects and rescue analgesic requirement were less in group-I than group-II.Also none of the patients experienced ketamine related side effects

CONCLUSION

We conclude that the addition of low dose (0.2mg/kg)epidural ketamine with bupivacaine and morphine accelerates the onset and duration of analgesia resulting in effective post operative analgesia in patients undergoing major abdominal surgeries without an increase in the incidence of side effects.

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										DRUG			HEART RATE											
s.no	name	age	sex	weight	diagnosis	surgery	ASA	GROUP	DUR. SX	TIME ADM	ONSET	DURATION-HRS	HR-BL	HR-0	HR-15min	HR-30min	HR-1	HR-2	HR-4	HR-6	HR-8	HR-12	HR-16	HR-20	HR-24
1	kandan	65	1	60	choledocholithiasis	open chole+CBD exp	2	1	120	10	5	12	90	88	85	78	76	74	80	84	82	90	92	94	92
2	malar	55	2	65	incisional hernia	mesh repair	1	1	120	60	7	11	88	88	81	82	78	83	88	82	84	90	84	90	92
3	ellammal	27	2	60	incisional hernia	abdominoplasty	1	1	150	90	5	16	88	86	82	83	76	74	78	80	78	76	80	88	92
4	venkatesan	44	1	60	incisional hernia	mesh repair	1	1	180	30	7	18	84	80	77	74	78	80	82	76	78	82	77	92	88
5	chinnadurai	38	1	60	renal cyst	nephrectomy	2	1	150	30	8	6	88	94	86	84	82	80	82	95	78	74	76	86	84
6	kokilammal	65	2	58	cholelithiasis	open chole	2	1	140	60	7	13	84	88	84	78	68	64	70	72	68	70	84	74	78
7	kalaimohan	43	1	60	chr.calc.pancreatitis	frey's procedure	2	1	300	30	6	16	74	80	73	72	70	66	76	72	74	76	92	82	78
8	mohan	56	1	58	ileocae.stric/postilstmy	ileostomy closure	2	1	150	20	6	15	78	90	74	72	76	74	80	74	78	80	88	78	86
9	kumarasamy	42	1	56	GOO	GOO	2	1	120	20	5	15	90	98	90	88	84	88	86	78	78	77	94	82	84
10	kalimuthammal	52	2	45	GOO	lap TV,GJ &JJ	2	1	150	90	5	11	90	92	76	74	72	86	74	78	80	91	80	78	74
11	sakkarapani	45	1	54	cholelithiasis	openchole'c.duodenostomy	2	1	180	60	7	16	82	88	74	72	73	76	74	76	80	78	102	88	90
12	muniyammal	60	2	50	cholelithiasis	open chole	2	1	90	10	5	13	84	88	77	78	75	72	82	84	86	78	88	80	79
13	mathiazhagan	45	1	58	hydatid cyst-liver	lap and proceed	2	1	75	20	5	17	88	90	76	78	82	78	84	76	74	82	80	90	92
14	susan	45	2	61	cholelithiasis	open chole	2	1	90	30	5	18	88	78	70	73	74	76	72	74	76	72	76	90	70
15	syed fathima	56	2	55	cholelithiasis	open chole	2	1	120	45	6	15	78	90	76	74	88	72	76	71	75	78	106	88	72
16	malliga	35	2	58	pseudocyst-pancreas	cystogasterostomy	1	1	180	75	10	17	102	90	76	82	76	74	75	82	82	77	96	80	84
17	vadivel	50	2	54	GOO	lap TV,GJ &JJ	1	1	150	90	6	14	82	92	88	86	73	74	76	74	80	79	86	88	74
18	kanchana	32	2	60	GOO	lap TV,GJ &JJ	2	1	180	60	8	17	92	82	68	64	74	76	78	77	75	81	82	83	94
19	subramani	50	1	62	GOO	lap TV,GJ &JJ	2	1	180	60	5	14	80	90	84	82	86	80	78	76	80	82	86	78	90
20	rajathi	34	2	52	GOO	lap TV,GJ &JJ	2	1	120	90	5	15	82	88	86	80	78	74	78	80	73	76	88	86	72
21	raja eswaraiya	39	1	58	pseudocyst-pancreas	cystogasterostomy	1	1	180	75	8	13	84	90	84	78	82	80	74	76	72	78	84	90	112
22	nagappan	54	1	60	incisional hernia	mesh repair	1	1	150	45	6	18	80	90	82	80	76	78	74	71	72	90	80	74	90
23	venkatammal	55	2	58	cholelithiasis	open chole	1	1	180	60	5	13	82	88	78	74	80	71	68	64	78	71	90	96	71
24	rathinam	64	1	54	post GJ status	roux-en-y	2	1	150	30	6	12	80	96	76	78	74	72	68	73	71	91	92	75	78
25	amudha	37	2	55	chr.calc.pancreatitis	frey's procedure	1	1	240	40	7	14	74	90	74	72	80	82	86	82	70	75	90	76	104
26	mani	44	1	60	incisional hernia	mesh repair	1	1	150	40	5	12	74	90	78	72	70	69	75	72	70	76	90	92	74
27	veerappan	43	1	58	hydatid cyst-liver	lap and proceed	1	1	120	60	6	15	78	86	74	71	80	81	76	75	71	73	87	92	102
28	gowri	33	2	54	cholelithiasis	open chole	1	1	120	60	5	10	72	92	78	74	73	71	80	82	68	93	102	116	76
29	selvi	40	2	56	incisional hernia	abdominoplasty	1	1	180	30	7	9	84	104	92	80	78	74	80	82	99	70	92	96	78
30	gomathi	42	2	58	incisional hernia,appen	abdominoplasty,appen	1	1	135	20	5	7	80	90	74	82	78	72	72	71	90	102	78	72	92
31	jahida	40	2	54	inci-her&paraumbli-her	ana-repair	1	2	160	15	10	10	88	90	82	77	86	78	80	83	81	82	106	92	80
32	palani	55	1	60	ben-pancr-tumour	whipple'procedure	2	2	270	15	15	9	64	84	68	70	71	72	80	75	76	99	87	88	90
33	selvi	50	2	65	incisional hernia	ana-repair	1	2	180	60	9	8	90	112	82	86	81	77	78	74	78	82	86	90	76
34	vanitha	19	2	45	ben-ova-tumour	exp-laparotomy	1	2	90	120	10	10	90	86	84	77	71	74	78	75	76	81	92	100	74
35	kasthuri	35	2	48	jeju-intussuception	lap& proceed	1	2	210	30	12	8	74	94	78	79	80	81	82	83	84	103	80	90	92
36	kulanjinathan	50	1	60	GOO	lap TV,GJ &JJ	1	2	185	30	12	7	74	96	90	78	80	74	72	70	91	90	112	80	78
37	paulraj	33	1	60	pseudocyst-pancreas	cystogasterostomy	1	2	155	25	15	7	88	90	78	70	74	73	72	70	80	88	104	84	78
38	jayalakshmi	50	1	61	hypo-gast-mass&inci-her	TAH,BSO,anat-repair	1	2	200	40	10	9	90	94	82	80	81	78	76	80	81	91	78	90	93
39	mariyammal	60	2	80	inci-her&ventral-her	anat-repair	2	2	100	20	10	8	78	98	77	70	71	72	83	70	74	99	120	90	87
40	ramasamy	32	1	56	goo	lap TV,GJ &JJ	2	2	190	120	10	9	9	80	72	78	71	72	74	76	74	88	90	76	76
41	sivamani	56	2	58	GOO	lap TV,GJ &JJ	2	2	175	50	15	8	72	92	74	76	78	80	82	72	77	82	85	90	88
42	chinnasamy	25	1	58	cholelithiasis	open chole	1	2	160	120	12	7	90	98	81	82	86	84	83	77	91	92	88	74	71
43	indhirani	41	2	54	cholelithiasis	open chole	1	2	135	45	14	9	80	81	77	75	78	80	72	71	76	80	96	118	78
44	krishnaveni	58	2	57	incisional hernia	anat-repair	1	2	170	90	15	8	78	86	74	74	77	72	72	71	74	80	92	88	82
45	mary	54	2	72	cholelithiasis	open chole	2	2	130	70	10	8	80	78	75	72	80	82	75	77	72	90	74	73	88
46	harilakshmi	50	2	58	ben-ova-tumour	lap& proceed	1	2	120	45	13	9	80	88	77	76	77	74	80	71	72	90	88	74	72
47	sheik	24	1	56	pseudocyst-pancreas	cystogasterostomy	1	2	180	30	15	8	76	88	74	76	78	75	76	74	76	90	91	87	75
48	adhiyammal	51	2	58	choledocholithiasis	CBD-exp,duo-jujunostomy	1	2	190	40	13	9	74	80	78	71	76	70	72	75	77	87	89	98	72
49	anandhi	38	2	54	chr.calc.pancreatitis	frey's procedure	1	2	240	60	13	10	82	88	76	77	75	74	71	72	73	74	106	102	77
50	kamatchi	40	2	58	cholelithiasis	open chole	1	2	150	25	14	8	72	71	80	80	77	74	70	74	75	95	96	76	112
51	murugan	40	1	61	hydatid cyst-liver	lap& proceed	1	2	100	40	15	6	80	82	72	70	72	71	73	74	86	90	92	94	72
52	samikannu	52	1	56	incisional hernia	anat-repair	2	2	135	80	12	7	88	108	86	81	82	88	76	75	90	88	89	91	88
53	kulanjiappan	38	1	62	GOO	lap TV,GJ &JJ	1	2	150	65	10	8	90	100	92	87	85	82	81	77	90	96	98	99	73
54	sudha	30	2	55	cholelithiasis	open chole	1	2	120	40	15	6	71	78	68	72	78	77	76	72	90	112	78	76	75
55	vedamaragatham	42	2	63	incisional hernia	anat-repair	1	2	145	40	13	8	70	86	80	72	74	80	77	75	78	88	89	93	77
56	manickam	48	1	59	pseudocyst-pancreas	cystogasterostomy	1	2	160	20	15	10	70	82	78	68	80	78	77	76	75	73	80	90	92
57	ramamoorthi	42	1	64	incisional hernia	anat-repair	1	2	145	10	15	9	70	78	77	74	72	77	75	77	78	87	88	108	78
58	vanitha	38	2	52	cholelithiasis	open chole	1	2	135	50	12	8	71	88	75	71	73	76	74	73	75	92	77	96	71
59	mohammed	30	1	60	ccp	frey's procedure	1	2	235	35	10	9	78	72	74	80	71	72	73	75	80	90	88	87	92
60	riyas	28	1	54	pseudocyst-pancreas	lap TV,GJ &JJ	1	2	130	40	12	8	83	90	81	77	75	73	71	73	88	92	90	86	80

MASTER CHART

SYSTOLIC BLOOD PRESSURE													DIASTOLIC BLOOD PRESSURE												MEAN BLOOD PRESSURE			
SBP-BL	SBP-0	SBP-15m	SBP-30	SBP-1	SBP-2	SBP4	SBP-6	SBP-8	SBP-12	SBP-16	SBP-20	SBP-24	DBP-BL	DBP-0M	DBP-15M	DBP-30M	DBP-1	DBP-2	DBP-4	DBP-6	DBP-8	DBP-12	DBP-16	DBP-20	DBP-24	MBP-BL	MBP-0M	MBP-15M	MBP-30M
140	142	130	124	124	128	126	120	112	110	124	130	130	74	90	80	80	80	80	78	82	80	78	92	84	82	96	107	97	95
130	136	110	104	110	112	120	124	120	130	132	128	126	80	88	86	82	76	76	72	72	80	84	84	88	90	97	104	94	89
130	132	128	122	122	120	120	118	110	112	118	122	130	70	74	72	70	68	70	72	70	72	68	70	80	82	90	93	91	87
120	130	128	126	120	118	110	114	110	112	118	126	124	80	86	82	80	80	78	74	74	76	74	74	80	82	93	101	97	95
124	120	118	116	118	110	108	108	112	120	126	112	120	84	88	84	84	82	78	70	72	75	82	80	72	68	97	99	95	95
114	120	110	106	104	110	112	114	110	106	134	110	112	72	80	70	68	70	70	70	72	70	72	74	72	76	86	93	83	81
140	130	120	120	118	118	112	114	112	110	124	130	124	74	80	78	78	76	76	74	78	76	78	78	72	80	96	97	92	92
124	130	124	114	110	106	110	110	106	104	112	116	126	82	90	70	70	68	70	70	72	70	72	80	78	84	96	103	88	85
96	120	110	106	102	102	106	108	106	108	120	110	112	64	90	70	72	68	72	64	66	70	70	78	74	76	75	100	83	83
140	130	122	118	118	114	110	108	110	132	124	122	118	82	100	82	84	82	76	78	76	78	82	86	83	78	101	110	95	95
110	120	106	108	108	112	110	112	112	108	114	112	122	70	82	76	76	74	74	76	72	70	72	78	88	80	83	95	86	87
140	136	128	122	120	118	110	110	114	116	132	138	130	80	80	78	76	76	78	72	74	72	74	73	84	73	100	99	95	91
130	136	120	112	110	112	110	112	110	112	110	134	120	74	82	80	76	76	80	76	74	72	70	72	86	74	93	100	93	88
132	128	122	110	112	110	112	114	110	112	116	132	120	88	84	82	78	78	76	74	76	72	78	76	84	82	103	99	95	89
142	136	124	110	112	110	110	112	110	108	124	124	110	80	90	76	76	78	74	68	70	70	72	82	78	82	101	105	92	87
144	130	124	122	120	120	118	110	112	110	108	112	136	84	88	78	78	76	72	76	76	76	74	78	86	76	104	102	93	93
110	130	122	120	118	114	110	110	108	110	128	122	126	72	86	76	74	76	74	74	74	72	72	84	88	74	85	101	91	89
110	108	102	100	102	100	102	100	102	100	104	102	110	76	80	78	76	78	74	74	76	76	72	74	82	68	87	89	86	84
130	132	120	120	116	116	118	112	116	112	122	114	112	86	82	72	74	72	76	76	74	76	74	80	84	80	101	99	88	89
124	130	122	120	120	116	112	114	112	108	118	124	108	82	92	80	74	74	76	74	76	70	68	80	78	72	96	105	94	89
138	136	130	124	120	114	112	110	112	110	138	132	104	92	90	88	86	86	82	80	78	76	78	96	92	78	107	105	102	99
120	130	122	120	112	110	110	112	110	110	112	130	116	74	98	74	74	72	74	76	76	74	70	76	82	78	89	109	90	89
132	130	122	118	118	116	116	116	110	112	124	130	118	88	82	80	80	78	76	74	76	76	78	76	88	80	103	98	94	93
134	140	124	122	112	110	111	110	110	112	122	108	132	70	92	80	78	76	74	76	74	74	76	102	86	76	91	108	95	93
120	134	114	110	112	110	110	106	104	108	122	130	104	70	80	74	74	72	72	72	60	64	64	80	84	88	83	98	87	86
134	128	122	114	110	102	104	104	100	118	122	124	130	70	88	80	80	74	72	74	72	70	68	82	80	88	91	101	94	91
110	132	120	110	108	110	110	108	110	112	110	110	110	72	86	80	76	76	74	72	70	68	66	68	68	74	85	101	93	87
120	134	130	128	118	118	116	110	112	120	128	132	122	82	96	88	76	76	74	74	74	72	82	90	76	80	95	109	102	93
144	138	120	118	116	110	112	110	120	132	142	126	120	90	100	88	80	70	72	72	70	70	92	78	74	82	108	113	99	93
98	112	110	110	108	108	106	108	114	120	102	124	106	64	84	70	68	70	72	70	68	66	68	82	86	78	75	93	83	82
114	130	110	112	110	108	106	106	106	112	120	125	132	68	88	70	72	70	68	70	70	68	70	88	90	82	83	102	83	85
130	146	126	120	118	110	110	114	120	140	132	120	118	88	96	74	74	74	70	70	72	86	90	72	74	80	102	113	91	89
130	150	122	118	112	114	112	110	130	121	120	112	130	88	78	78	70	72	72	70	72	90	96	92	76	74	102	102	93	86
124	130	112	110	112	110	110	112	112	120	118	130	132	78	90	74	76	74	76	74	72	72	90	80	78	76	93	103	87	87
142	132	130	128	124	124	124	120	122	138	140	124	120	86	96	84	80	78	78	77	78	78	90	82	84	82	105	108	99	96
132	130	124	120	120	118	118	114	112	132	122	118	120	88	90	86	84	82	80	80	78	76	80	90	86	80	103	103	99	96
136	126	120	120	114	114	110	112	110	112	108	112	134	72	88	80	78	78	74	74	74	74	72	74	86	90	93	101	93	92
120	130	122	112	110	112	112	110	132	106	126	120	118	86	94	80	80	78	78	76	74	80	88	76	74	90	97	106	94	91
138	124	118	114	116	114	110	108	106	136	110	114	112	92	86	80	78	78	76	76	76	74	92	88	80	78	107	99	93	90
140	130	128	122	116	118	114	112	132	140	112	132	106	74	84	74	76	76	74	76	74	72	86	90	88	74	96	99	92	91
120	118	110	110	110	110	112	110	118	132	124	110	128	76	88	68	66	64	68	70	70	70	80	82	90	74	91	98	82	81
128	128	114	116	116	112	108	110	108	132	120	124	118	74	82	76	74	72	74	74	72	72	84	88	78	74	92	97	89	88
114	124	120	120	118	118	110	110	114	124	132	128	124	70	80	78	78	74	72	74	74	76	80	92	86	84	85	95	92	92
128	124	112	114	110	108	110	110	108	128	124	122	120	76	84	80	80	76	76	70	70	70	90	96	80	72	93	97	91	91
110	122	120	114	110	108	110	110	112	128	134	120	124	80	88	86	76	74	70	70	72	72	90	92	82	76	91	99	97	89
134	128	122	110	112	108	106	108	110	124	134	138	110	70	82	80	80	78	76	78	78	76	86	98	78	76	91	97	94	90
120	122	124	110	112	110	112	110	132	136	130	128	122	70	78	70	72	72	70	72	70	80	88	80	84	88	87	93	88	85
122	120	114	110	112	110	108	110	132	120	132	128	110	70	76	74	74	72	74	74	72	90	86	92	78	74	87	91	87	86
130	134	124	114	112	114	110	112	112	132	128	142	112	76	86	74	74	76	74	72	74	72	90	88	86	72	94	102	91	87
108	112	110	110	108	110	110	110	116	130	132	124	130	70	82	76	74	76	74	72	70	86	88	98	74	72	83	92	87	86
114	120	112	110	108	110	110	110	132	138	112	128	114	68	84	70	70	72	72	72	74	74	80	90	74	72	83	96	84	83
124	138	120	120	110	108	110	110	110	112	130	108	132	70	92	72	70	72	72	70	72	74	90	92	94	80	88	107	88	87
110	122	120	118	110	112	110	110	108	122	128	132	134	80	76	74	74	70	70	68	70	72	80	76	84	82	90	91	89	89
120	130	112	110	112	108	102	106	110	120	124	132	110	72	90	72	72	70	70	72	72	70	92	78	74	74	88	103	85	85
126	130	122	112	118	118	110	110	112	140	112	132	120	76	78	70	70	68	68	70	70	72	72	76	82	90	93	95	87	84
118	124	110	110	110	110	112	110	120	130	118	124	122	72	78	70	68	64	68	66	68	72	68	86	90	80	87	93	83	82

MEAN ARTERIAL PRESSURE									VISUAL ANALOGUE SCALE											RAMSAY SEDATION SCALE									COMPLICATIONS						CUE ANALGESIC REQUIREME							
MBP-1	MBP-2	MBP-4	MBP-6	MBP-8	MBP-12	MBP-16	MBP-20	MBP-24	VR-0	VR-15M	VR-30M	VR-1	VR-2	VR-4	VR-6	VR-8	VR-12	VR-16	VR-20	VR-24	R-0	R-15M	R-30M	R-1	R-2	R-4	R-6	R-8	R-12	R-16	R-20	R-24	PONV	HYPO	BRADY	RES.DEP	PRU	DELIRIUM	2	4	6	8	12	16	20	24
95	96	94	95	91	89	103	99	98	3	1	1	1	1	1	1	1	1	3	3	4	2	2	2	2	2	2	2	3	2	1	1	0	0	0	0	0	0	nil	nil	nil	nil	nil	1	nil	1
87	88	88	89	93	99	100	101	102	3	1	1	1	1	1	1	1	3	3	3	4	1	2	2	2	3	3	3	2	2	1	2	2	0	0	0	0	0	0	0	nil	nil	nil	1	nil	1	1
86	87	88	86	85	83	86	94	98	3	1	1	1	1	1	1	1	1	2	3	3	2	2	2	2	2	2	2	2	2	2	2	1	0	0	0	0	0	0	0	nil	nil	nil	nil	nil	1	1
93	91	86	87	87	87	89	95	96	3	1	1	1	1	1	1	1	2	1	2	3	1	2	2	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	nil	nil	nil	nil	nil	1	nil
94	89	83	84	87	95	95	85	85	4	1	1	1	1	1	1	3	4	3	2	3	1	2	2	2	2	2	1	2	1	2	1	1	0	0	0	0	0	0	0	nil	nil	1	1	1	nil	1
81	83	84	86	83	83	94	85	88	3	1	1	1	1	1	1	1	1	3	2	4	1	2	2	2	2	2	2	2	2	2	1	1	0	0	0	0	0	0	0	nil	nil	nil	nil	1	nil	1
90	90	87	90	88	89	93	91	95	3	1	1	1	1	1	1	2	1	1	3	2	1	2	2	2	2	2	2	2	2	3	2	2	0	0	0	0	0	0	0	nil	nil	nil	nil	nil	1	nil
82	82	83	85	82	83	91	91	98	3	1	1	1	1	1	1	1	1	3	2	3	1	2	2	2	2	2	2	2	2	3	2	2	0	0	0	0	0	0	0	nil	nil	nil	nil	1		1
79	82	78	80	82	83	92	86	88	3	1	1	1	1	1	1	1	2	3	3	4	1	2	2	2	2	2	2	2	2	1	2	0	0	0	0	0	0	0	0	nil	nil	nil	1	1	nil	1
94	89	89	87	89	99	99	96	91	3	1	1	1	1	1	1	1	2	2	3	4	2	2	2	3	3	2	2	2	2	1	2	2	0	0	0	0	0	0	0	nil	nil	nil	nil	nil	nil	
85	87	87	85	84	84	90	96	94	3	1	1	1	1	1	1	1	1	2	2	4	1	2	2	2	2	2	2	3	3	2	1	2	0	0	0	0	0	0	0	nil	nil	nil	nil	nil	1	nil	1
91	91	85	86	86	88	93	102	92	4	1	1	1	1	1	1	1	1	4	3	2	1	2	2	2	2	3	2	2	2	2	1	1	0	0	0	0	0	0	0	nil	nil	nil	nil	1	1	nil
87	91	87	87	85	84	85	102	89	4	2	1	1	1	1	1	1	1	2	3	4	1	2	3	2	2	2	2	3	2	1	1	0	0	0	0	0	0	0	0	nil	nil	nil	nil	nil	1	nil
89	87	87	89	85	89	89	100	95	3	1	1	1	1	1	1	1	1	1	3	3	1	2	2	3	2	2	3	2	2	3	1	2	0	0	0	0	1	0	0	nil	nil	nil	nil	nil	1	nil
89	86	82	84	83	84	96	93	91	4	1	1	1	1	1	1	1	1	2	3	4	1	2	3	3	2	2	2	2	2	3	1	2	0	0	0	0	0	0	0	nil	nil	nil	nil	1	nil	1
91	88	90	87	88	86	88	95	96	3	1	1	1	1	1	1	1	1	2	4	3	1	2	2	2	3	2	2	2	3	2	1	2	0	0	0	0	0	0	0	nil	nil	nil	nil	nil	1	nil
90	87	86	86	84	85	99	99	91	3	1	1	1	1	1	1	1	1	2	3	4	1	2	2	3	2	2	2	2	3	2	1	2	0	0	0	0	0	0	0	nil	nil	nil	nil	1	1	nil
86	83	83	84	85	81	84	89	82	4	1	1	1	1	1	1	1	1	2	3	2	1	2	2	2	2	2	2	2	2	1	2	2	0	0	0	0	0	0	0	nil	nil	nil	nil	nil	1	nil
87	89	90	87	89	87	94	94	91	3	1	1	1	1	1	1	1	1	3	2	3	1	2	2	2	2	2	3	3	2	1	2	2	0	0	0	0	0	0	0	nil	nil	nil	nil	1	nil	1
89	89	87	89	84	81	93	93	84	4	1	1	1	1	1	1	1	1	3	3	2	1	2	3	2	2	2	2	2	3	1	2	2	0	0	0	0	0	0	0	nil	nil	nil	nil	1	nil	1
97	93	91	89	88	89	110	105	87	3	1	1	1	1	1	1	1	1	3	3	3	1	2	2	3	3	2	2	2	3	1	2	2	0	0	0	0	0	0	0	nil	nil	nil	nil	1	1	nil
85	86	87	88	86	83	88	98	91	3	1	1	1	1	1	1	1	1	2	2	3	1	2	3	3	2	2	2	2	2	2	1	2	0	0	0	0	0	0	0	nil	nil	nil	nil	nil	1	nil
91	89	88	89	87	89	92	102	93	4	1	1	1	1	1	1	1	1	5	3	2	1	2	2	2	2	2	2	1	2	2	3	0	0	0	0	0	0	0	0	nil	nil	nil	nil	1	1	nil
88	86	88	86	86	88	109	93	95	3	1	1	1	1	1	1	1	1	5	3	2	1	2	2	3	2	2	2	2	2	1	2	2	0	0	0	0	0	0	0	nil	nil	nil	nil	1	nil	1
85	85	85	75	77	79	94	99	93	4	1	1	1	1	1	1	1	1	4	3	2	1	2	3	2	2	2	2	2	1	2	3	1	0	0	0	0	0	0	0	nil	nil	nil	nil	1	1	nil
86	82	84	83	80	85	95	95	102	5	1	1	1	1	1	1	1	2	4	5	2	1	3	2	2	2	2	2	2	3	4	2	0	0	0	0	0	0	0	0	nil	nil	nil	1	nil	1	nil
87	83	81	80	81	81	92	95	100	4	1	1	1	1	1	1	1	1	2	4	3	1	2	2	3	2	2	2	2	1	2	2	2	0	0	0	0	0	0	0	nil	nil	nil	nil	nil	1	1
87	85	87	85	86	89	90	92	95	3	1	1	1	1	1	1	1	1	3	4	2	1	2	2	3	2	2	2	2	1	2	2	3	0	0	0	0	0	0	0	nil	nil	nil	nil	1	1	nil
83	85	83	83	84	91	92	99	91	4	1	1	1	1	1	1	1	1	4	2	2	1	2	3	3	2	2	2	2	1	2	2	1	0	0	0	0	0	0	0	nil	nil	nil	nil	1	nil	1
87	83	81	80	81	81	92	95	100	4	1	1	1	1	1	1	1	1	2	4	3	1	2	2	3	2	2	2	2	1	2	2	2	0	0	0	0	0	0	0	nil	nil	nil	nil	nil	1	1
87	85	87	85	86	89	90	92	95	3	1	1	1	1	1	1	1	1	3	4	2	1	2	2	3	2	2	2	2	1	2	2	3	0	0	0	0	0	0	0	nil	nil	nil	nil	1	1	nil
83	85	83	83	84	91	92	99	91	4	1	1	1	1	1	1	1	1	4	2	2	1	2	3	3	2	2	2	2	1	2	2	1	0	0	0	0	0	0	0	nil	nil	nil	nil	1	nil	1
85	86	87	86	94	104	93	92	95	4	1	1	1	1	1	1	3	4	2	3	2	1	3	2	2	2	2	2	1	2	2	1	2	0	0	0	0	0	0	0	nil	nil	nil	1	1	nil	1
83	85	84	85	86	95	102	96	95	4	1	1	1	1	1	1	1	1	4	2	2	2	1	1	2	2	3	2	2	2	1	2	1	2	0	0	0	0	0	0	nil	nil	nil	1	nil	1	
90	89	88	86	85	95	103	95	94	6	1	1	1	1	1	1	1	3	2	3	2	1	2	2	3	3	2	2	2	1	2	2	2	0	0	0	0	0	0	0	nil	nil	nil	1	nil		1
85	85	85	83	87	105	99	91	95	6	1	1	1	1	1	1	1	3	3	2	2	1	2	3	3	2	2	2	2	1	2	1	2	0	0	0	0	0	0	0	nil	nil	nil	1	nil	1	nil
83	84	82	81	82	85	89	99	87	3	1	1	1	1	1	1	1	1	2	3	2	1	2	2	3	2	3	3	2	1	2	2	2	0	0	0	0	0	0	0	nil	nil	nil	1	1	nil	nil
83	81	82	82	81	84	99	102	99	3	1	1	1	1	1	1	1	3	4	2	2	1	2	2	3	2	2	2	2	1	2	1	2	0	0	0	0	0	0	0	nil	nil	nil	1	1	nil	nil
89	83	83	86	97	107	92	89	93	4	1	1	1	1	1	1	2	4	3	2	2	1	2	2	3	3	2	2	1	2	3	2	1	0	0	0	0	0	0	0	nil	nil	1	nil	1	nil	1
85	86	84	85	103	104	101	88	93	3	2	1	1	1	1	1	2	2	3	2	2	1	2	2	2	2	2	1	2	1	2	2	0	0	0	0	0	0	0	0	nil	nil	1	nil	1	1	nil
87	87	86	85	85	100	93	95	95	3	1	1	1	1	1	1	1	2	4	2	2	1	2	3	3	2	2	2	2	1	2	3	2	0	0	0	0	0	0	0	nil	nil	nil	nil	1	nil	1	nil
93	93	93	92	93	106	101	97	95	4	1	1	1	1	1	1	1	2	5	2	2	1	2	3	2	2	2	2	2	1	2	3	1	0	0	0	0	0	0	0	nil	nil	nil	nil	1	nil	1	nil
95	93	93	90	88	97	101	97	93	3	1	1	1	1	1	1	1	3	2	4	2	1	2	2	2	2	2	2	1	2	2	2	0	0	0	0	0	0	0	0	nil	nil	nil	nil	1	nil	1	nil
90	87	86	87	86	85	85	95	105	3	2	1	1	1	1	1	1	3	5	2	2	1	2	2	3	2	2	2	2	1	2	3	2	0	0	0	0	0	0	0	nil	nil	nil	nil	1	nil	1	nil
89	89	88	86	97	94	93	89	99	3	1	1	1	1	1	1	2	3	4	2	2	1	2	2	2	3	2	3	1	2	2	2	1	0	0	0	0	0	0	0	nil	nil	1	nil	1	nil	1
91	89	87	87	85	107	95	91	89	4	1	1	1	1	1	1	1	3	4	2	2	1	2	3	3	2	2	2	2	1	2	2	2	0	0	0	0	0	0	0	nil	nil	nil	1	nil	1	nil
89	89	89	87	92	104	97	103	85	4	2	1	1	1	1	1	1	3	2	3	2	1	2	2	3	2	2	2	2	1	2	2	3	0	0	0	0	0	0	0	nil	nil	nil	1	nil	1	nil
79	82	84	83	86	97	96	97	92	4	1	1	1	1	1	1	1	3	2	4	2	1	2	2	3	3	2	2	2	1	2	1	2	0	0	0	0	0	0	0	nil	nil	nil	nil	1	nil	1	1
87	87	85	85	84	100	99	93	89	3	1	1	1	1	1	1	1	3	4	3	2	1	2	3	3	2	2	2	2	1	2	2	2	0	0	0	0	0	0	0	nil	nil	1		1	nil	1
89	87	86	86	89	95	105	100	97	4	2	1	1	1	1	1	1	2	4	2	2	1	2	2	3	2	2	2	2	1	2	3	2	0	0	0	0	0	0	0	nil	nil	nil	1	nil	1	nil
87	87	83	83	83	103	105	94	88	3	1	1	1	1	1	1	1	3	4	2	2	1	2	2	3	3	2	2	2	1	2	2	2	0	0	0	0	0	0	0	nil	nil	nil	1	nil	1	nil
86	83	83	85	85	103	106	95	92	4	1	1	1	1	1	1	1	1	3	2	2	1	2	2	3	3	2	2	2	1	2	1	2	0	0	0	0	0	0	0	nil	nil	nil	nil	1	nil	1	nil
89	87	87	88	87	99	110	98	87	3	1	1	1	1	1	1	1	4	2	2	2	1	2	3	2	2	2	2	3	1	2	2	3	0	0	0	0	0	0	0	nil	nil	1	nil	1	nil	1
85	83	85	83	97	104	97	99	99	5	2	1	1	1	1	1	2	5	4	3	2	1	2	3	2	3	2	2	2	1	2	1	1	0	0	0	0	0	0	0	nil	nil	1	1	nil	1	nil
85	86	85	85	104	97	105	95	86	4	1	1	1	1	1	1	3	5	3	2	3	1	2	2	3	2	3	3	2	2	1	2	2	0	0	0	0	0	0	0	nil	nil	1	1	nil	1	nil
88	87	85	87	85	104	101	105	85	5	1	1	1	1	1	1	3	4	2	2	1	2	2	2	2	2	3	2	2	1	1	2	0	0	0	0	0	0	0	0	nil	nil	nil	1	nil	1	nil
87	86	85	83	96	102	109	91	91	3	2	1	1	1	1	1	2	3	4	3	2	1	2	2	2	2	2	2	1	2	1	2	0	0	0	0	0	0	0	0	nil	nil	1	nil	1	nil	1
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85	84	83	85	86	97	105	99	97	3	1	1	1	1	1	1	1	1	2	4	2	1	2	2	3	2	3	3	2	2	2	1	1	0	0	0	0	0	0	0	nil	nil	nil	1	nil	1	nil
83	84	82	83	84	94	93	100	99	4	2	1	1	1	1	1	1	2	3	3	2	1	2	3	3	2	2	2	2	1	2	3	3	0	0	0	0	0	0	0	nil	nil	nil	1	1	nil	1
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